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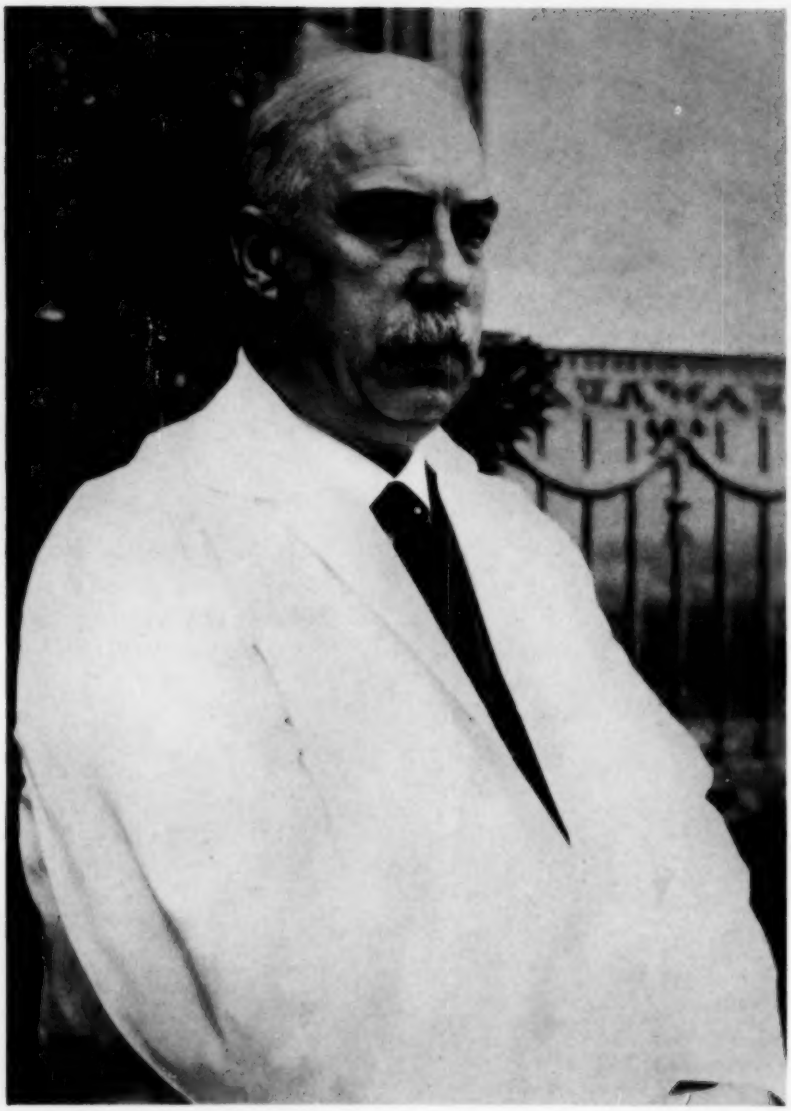

Dr. J. G. Dusser de Barenne
(Kindness of Dr. Paul E. Rekers)

J. G. DUSSER DE BARENNE 1885–1940

THE *Journal* records with deep sorrow the death of the senior member of its Editorial Board. Dr. Dusser de Barenne after repeated attacks succumbed during a coronary seizure at the Deaconess Hospital in Boston on the afternoon of June 9th, a few days after his 55th birthday.

Joannes Gregorius Dusser de Barenne, one of the foremost physiologists of our time, was born at Brielle in The Netherlands, June 6, 1885, the son of Elize M. Dusser de Barenne, a municipal official in Amsterdam, by his wife, Dorothea Vogelzang. After preliminary education in Dutch public schools, Dusser de Barenne entered Amsterdam University where he received his medical qualifications in 1909. On October 12, 1911, he married Kate Snellen, daughter of the Dutch ophthalmologist, successor to the great ophthalmic surgeon, Franz C. Donders. There were three children, Charlotte (Mrs. Crosby Greene, Jr.), Dorothea and Elizabeth. Shortly after their arrival in the United States, Mrs. Dusser de Barenne died in Ithaca, New York, May 8, 1931, while accompanying her husband on a lecture trip. In 1935 Dusser de Barenne married Emily Lockwood Greene, daughter of Dr. D. Crosby Greene of Boston. There is one child, Marion, by this marriage.

Dusser de Barenne's career as a scientific investigator fell into five periods.* The first, between 1909 and 1911, was spent as teaching assistant in the Laboratory of Physiology at Amsterdam in a capacity equivalent to that of an Instructor. During these years, he began to investigate the physiological action of strychnine on the central nervous system, his first studies dealing with the effect of local application of strychnine on the reflexes of the spinal cord (1,2,3). Seven of the nine papers published during these two years, had to do with the effects of strychnine. Although his attention was first concentrated upon the action of strychnine *per se*, Dusser de Barenne quickly grasped the potentialities of the drug as a tool for investigation of the activity of the nervous system, and in later years he used the alkaloid in connection with many of his most fundamental studies of nervous function.

The second phase of his scientific career extended from September 1911 until the outbreak of the first world war in August 1914, during which time he held the post of psychiatrist to the Meerenberg Lunatic Asylum north of Amsterdam. In these years, he continued in the experimental field and also published papers on various aspects of organic neurology. His physiological studies were, for the most part, concerned with elucidating the phenomenon of decerebrate rigidity, earlier described by Sherrington (11). Among other things, he established the fact that well-defined action cur-

* A complete list of Dr. Dusser de Barenne's scientific papers follows this appreciation.

rents can be detected in muscles exhibiting the rigidity of the decerebrate state. He also devoted attention to the neck and labyrinthine reflexes which had recently been described by Magnus and de Kleyn, pointing out that their presence could be detected in animals with an intact nervous system (16).

During the third phase of Dusser de Barenne's scientific activities from August 2, 1914, to April 28, 1918, while serving as medical officer on active duty in the Dutch Army, he found time to study the mechanism of tonic contraction of skeletal muscle (19, 21), as well as the functional localization of sensory phenomena in the cerebral cortex (18). With J. Boeke, he published a paper on sympathetic innervation of skeletal muscle (25), and despite the heavy responsibilities of military service, he was able during this unsettled period to prepare ten important scientific papers.

Dusser de Barenne left the army just before the cessation of the first world war to accept an appointment as Lecturer and Privat Dozent in the Departments of Pharmacology and Physiology at Utrecht University, a post which he held from May 1918 until September 1930. During these years, he was in intimate contact with one of the foremost contributors to the literature of neurophysiology, Rudolph Magnus. He joined Magnus in a study of the physiology of posture (29), and also gave attention to the functions of the cerebellum; but his interests were catholic, for in addition to the subjects just mentioned, one finds papers on the action of insulin (42), on the metabolism of muscles during decerebrate rigidity (43), on the influence of the vagi on action currents of the diaphragm (39), and several papers on nystagmus (48, 61).

His most important contribution during these years came as a result of a visit in the spring of 1924 to the Laboratory of Sir Charles Sherrington at Oxford. There he studied the sensory symptoms which followed the local application of strychnine to the cerebral cortex of rhesus monkeys. The paper embodying these findings published in the *Proceedings of the Royal Society* in 1924 (vol. 96B, pp. 272–291) entitled "Experimental researches on sensory localization in the cerebral cortex of the monkey (Macacus)" is now a classic. It demonstrated for the first time the major functional subdivisions of the sensory cortex, *i.e.*, the areas for the leg, arm and face; the paper was the first of an important series on functional localization in the cerebral cortex.

By this time, Dusser de Barenne had, by common consent, become the foremost of the younger generation of Dutch physiologists. With the deaths of Willem Einthoven and Rudolph Magnus, both in 1927, and the retirement of Hendrik Zwaardemaker, the three most important chairs of Physiology and Pharmacology became vacant in Holland almost simultaneously. Any one of them Dusser de Barenne would have filled with distinction, and he no doubt would have been called to one of them had it not been for religious restrictions in the Dutch universities, which were intolerable to a free-thinker of Dusser de Barenne's outspoken tendencies. And so it came

to pass that Holland allowed the United States to claim one of the most distinguished physiologists the continent of Europe has ever produced.

The three chairs just mentioned had all been filled by the autumn of 1928, and in the spring of 1929 Dean Winternitz travelled to Utrecht hoping to persuade Dusser de Barenne to come to the Yale School of Medicine. The International Physiological Congress was being held that summer in Boston (August 19–24, 1929) and the International Psychological Congress a week later in New Haven (September 1–4, 1929). Dusser de Barenne attended both meetings, and shortly after his return to Europe decided to come back to New Haven in a year's time to establish a research laboratory in the field of neurophysiology.

Professor Dusser de Barenne arrived in New Haven with his family on September 24, 1930, but since the extension of the Sterling Hall of Medicine in which his laboratory quarters were to be placed was then in process of construction he spent his first year in temporary quarters in the Brady Laboratory. His first collaborator at Yale was Clyde Marshall, with whom he described a release-phenomenon induced by isolating a focus of the motor cortex from adjacent cortical areas (66); his second collaborator was Stephen Brody, with whom he studied the effects of hyper-ventilation on excitability of the cortex (71). These two papers inaugurated a series of highly important studies on the functional organization of the cerebral hemispheres in primate forms. With David Koskoff he discovered the phenomenon of flexor rigidity (72, 81) in spinal cats (1931–33). Richard Wendt also carried out studies on conditioned reflexes in his Laboratory in 1933–35 and Dusser de Barenne often referred to the valuable improvements in systems of recording which Wendt introduced.

In 1934 a fruitful collaboration was begun with Warren S. McCulloch, who for six years has been his devoted and congenial colleague in research. Joined later by Leslie Nims, Carl Hovland and others, a team developed which demonstrated the reciprocal relationships between the activity of the cortex and its hydrogen-ion concentration. The research program inaugurated by Dusser de Barenne at Yale thus proceeded in the most logical manner from the release phenomenon discovered with Marshall to the effects on excitability in hyperventilation studied with Brody, to the new technique of laminar destruction of cortical cell layers with Zimmerman, the study of excitability cycles and the discovery of the phenomenon of "extinction" with McCulloch, and the pathological changes following laminar coagulation. The program culminated in the correlation of these phenomena with changes in the hydrogen-ion concentration (studied with Nims and McCulloch).

With these basic correlations established, it was possible to study two general problems: (i) the influence of one cortical area upon another, and (ii) the interaction between the cerebral cortex and the thalamus, and between the cerebral cortex and the basal ganglia. It is in the last phase of this work that Dusser de Barenne and his colleagues have been engaged

during the past two years. In 1939–40, with Percival Bailey, Hugh W. Garol, William E. Stone and Craig W. Goodwin, they had extended their studies to the chimpanzee.

In reviewing Dusser de Barenne's work, one becomes aware that there are few parallels in the history of physiology to his sustained productivity, especially during his later years. It culminated during the last ten in one of the most important series of physiological papers to emanate in a corresponding interval from the pen of one man.

In his physiological work Dusser de Barenne developed many new techniques such as the strychnine method for localization of sensory function, laminar coagulation for analysis of the cortical layers, and the adaptation of electrical techniques for study of the interaction of specific cortical areas. He will be remembered for his unyielding faith in the experimental method and for his utter intolerance of those who place the armchair ahead of the experimental table as a place for solving the problems of physiology—"never think, if you can experiment." He was a man of strong personality and strong loyalties, and in greeting a stranger he often seemed to regard him as a scheming, insincere fellow until he had proved himself otherwise. This accounted for his proverbial caution with visitors and for humorous anecdotes that his many friends enjoy relating. But once anyone had proved himself worthy of Dusser de Barenne's friendship, the attitude and the friendship never altered.

In his personal life, he was reticent and never discussed his personal affairs outside the ranks of his immediate family. He was widely read in music, in art and in philosophy past and present, and he was essentially a Kantian in his outlook. He had a number of heroes. Among these was Claude Bernard, whose portrait was always before him on his desk; another was Carl Ludwig; and the third was his Chief at Utrecht, Rudolph Magnus. These were men of action, men of experiment, who never allowed their deductions to usurp the place of experiment.

The School of Medicine at Yale will also remember Dusser de Barenne as a teacher. While he had no formal obligation to teach in the School of Medicine, he offered each year one or two electives, on the sense organs, or on special phases of the physiology of the central nervous system. Almost invariably he illustrated the lectures by experimental demonstrations into which he put much time and thought, and usually he ended these amusing and informative discussions in a fever heat of perspiration. The students responded with great warmth of appreciation, for these were lectures unique in their medical experience.

As an editor of this *Journal*, he rendered an incalculable service, originally in formulating its policies, and during the three years since it was conceived. His editorial judgments were wise and just and they were always set down in terse and unmistakable language; while he read all manuscripts carefully, he reached his editorial decisions so quickly that papers rarely

remained on his desk more than 24 hours. His loss to the *Journal*, as well as to physiology in its broadest sense, is irreparable.

Ave atque vale!

J. F. F.
R.W.G.

June 10, 1940

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V. NEW HAVEN
Laboratory of Neurophysiology
Yale University School of Medicine
October 1, 1930–June 9, 1940

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Dr. Dusser de Barenne left some ten additional papers in preparation.

HYPOTHALAMIC LESIONS AND PNEUMONIA IN CATS

With Notes on Behavior Changes

E. W. HAERTIG and JULES H. MASSERMAN
Division of Psychiatry, Department of Medicine and the Otho S. A. Sprague Memorial Institute, University of Chicago

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During the course of a series of experiments in which the effects of extensive hypothalamic lesions in cats were studied, a large proportion of the animals succumbed to bronchopneumonia within the first postoperative week (1). It is our present purpose to report upon an investigation of this phenomenon.

METHODS

Forty adult cats were operated upon as follows: Each animal was anesthetized with nembutal, the skull trephined, and the Horsley-Clarke apparatus mounted (2, 3). An electrode was then inserted stereotactically so that 3 or 4 vertical punctures spaced 2 mm. apart in a rostro-caudal plane were made into the hypothalamus. At from 2 to 4 points in the course of each puncture a direct current of from 3 to 4 mA was passed for 40 sec. in order to coagulate the surrounding nerve tissue. In separate series of animals the lesions were placed as follows: The rostral lesions (5 cats) extended from the anterior commissure to the caudal margin of the optic chiasm; the middle (27 cats) from the caudal border of the chiasm (which was not destroyed) through the tuber cinereum into the mammillary bodies; and the caudal (8 cats) from the middle level of the mammillary bodies into the mesencephalon to the rostral margins of the red nuclei. In all cases the regions destroyed extended medially to within 0.5 mm. of the ventricular surface, laterally for 3 to 4 mm. and dorsad for from 3 to 6 mm. from the base of the brain. Immediately after operation the animal was transferred to a constant temperature room (92°F.), where it remained continuously except for daily periods of laboratory observation of from 30 to 60 min. at about 75°F. After from 1 to 24 days of observation the animal was autopsied and the brain and viscera removed for microscopic examination.

Eight of the 27 animals with middle hypothalamic lesions died before the 5th postoperative day from such causes as thrombosis of the circle of Willis, brain abscess or meningitis and were therefore eliminated from the series. The remainder (32 cats) are classified as (i) survivals, including cats which presumably would have lived indefinitely had they not been sacrificed and a small number which died 5 or more days postoperatively of causes other than pneumonia; and (ii) animals in which bronchopneumonia was found to be the cause of death. The 32 animals were therefore distributed with respect to site of lesion as follows: rostral, 5 cats; middle, 19 cats; and caudal, 8 cats.

Results

Rostral lesions: Animals with such lesions often sought the investigator's attention and were responsive to fondling, although two proved unusually aggressive toward dogs and other cats. All 5 animals survived and none showed polydipsia, polyuria nor appreciable loss of temperature regulation.

Middle lesions—General behavior. The animals with these lesions were lethargic and had some degree of extensor hypertonicity for varying periods after operation. When left undisturbed, they usually showed no affective behavior and were equally indifferent to food, rats, and dogs. Nevertheless, they were able to defend themselves effectively with teeth and claws against

tube feeding and restraint, although movements were not as efficient nor as well integrated as those of normal animals. They responded to stroking by arching of the back, but purring could not be elicited. When subjected to exceptionally aggressive attacks by other cats or by dogs they defended themselves in the supine posture typical for combat in close quarters; when thus aroused they remained alert for a short time and forestalled further engagements by hissing, growling, and striking out with extended claws. When held upright by the nape of the neck with hind paws touching the floor, animals with middle lesions often tried to leap high into the air and to claw wildly until again set upon all fours, after which they ran aimlessly away. Several such animals, provided with a corner of coarse screening, repeatedly climbed as much as 4 feet above the floor and resisted all efforts to dislodge them, although they ultimately dropped off and once on their feet scampered away. After about a week the long-term animals of this group began to recover from their lethargy, to regain their temperature control and behave more nearly like normal animals. However, the other 16 lived only an average of 3.5 (range 1 to 8) days, and followed a gradually declining course characterized by increasing malaise, a rising temperature and the physical signs of widespread bronchopneumonia.

Temperature regulation. All animals with middle hypothalamic lesions were relatively poikilothermic, their body temperatures falling from 1.5 to 4.7°F. during 30 min. of exposure in the laboratory. Nevertheless, absolute poikilothermia did not occur, since no animal had a body temperature below 99.8° while in the incubator at 92°, whereas the lowest temperature recorded in the entire series was 91.4° in a cat which had remained 36 hours at a maximum temperature of 78°. Furthermore, twelve of the partially poikilothermic animals were able to respond to pneumonic and other infections with a fever of 104°, 7 above 105.5°, 4 of 107° and one as high as 108°. In general, the higher the fever the greater the rate of fall in body temperature when the animal was removed from the incubator. Shivering and abnormal panting occurred in 2 animals but no instance of neurogenic fever was observed.

Caudal lesions. Animals with such lesions manifested varying degrees of catalepsy and muscular hyperreflexia, but these diminished after the first postoperative week in the 6 animals which survived. One of the remaining 2 cats died on the 7th day after the experimental administrations of massive doses of benzedrine sulphate; the other, who succumbed to pneumonia after 7 days, was the only animal with a caudal lesion which was definitely poikilothermic. However, one of the surviving animals had a ("neurogenic"?) fever of from 103 to 107°F. for 11 days before sacrifice; at autopsy no explanation for the pyrexia could be found.

DISCUSSION

Etiologic factors in pneumonia. The strikingly high incidence of pneumonia in the cats with middle hypothalamic lesions led to the consideration of the following possible etiologic factors: (i) pre- or postoperative distemper,

(ii) effects of anesthesia; (iii) aspiration; (iv) septic pulmonary emboli from the operative or other infected site; (v) laryngeal obstruction; (vi) gastrointestinal disturbances; (vii) exposure to artificial extremes of temperature; (viii) hemorrhage about the brain lesion; (ix) cardiovascular collapse; and (x) loss of normal temperature regulation.

Distemper. Care was taken to select cats free from all types of infection, respiratory or otherwise. Only two animals developed postoperative upper respiratory infections and both survived.

Anesthesia. Light nembutal anesthesia (0.02 to 0.03 gm. per kg. intraperitoneally) was used in all operations and therefore remained a constant factor. Furthermore, in another series of over 200 recovery animals in which the same anesthetic was used in performing non-destructive hypothalamic operations, the eight-day mortality rate was less than 4 per cent, as compared to 85 per cent in cats with middle hypothalamic lesions.

Aspiration. Certain general measures were taken in all of the experiments to prevent aspiration. During operation the rear end of the cat board was elevated and for the next 24 hours, during which time aspiration was most likely to occur, the cat was strapped head lowermost into a specially constructed and tilted cage. All animals were maintained for 24 hours before and after operation solely by the intraperitoneal injections of 10 per cent dextrose in Ringer's solution, and feeding was not resumed until the animal could again swallow normally. All the animals with hypothalamic lesions coughed vigorously when a foreign body entered the trachea, indicating that this safeguard against aspiration had not been abolished. Further to control the possibility of the aspiration of saliva, enough atropine to prevent salivation (usually 6 mg.) was given to 5 cats about 30 min. before they were anesthetized and repeated until deglutition and coughing had returned to normal; nevertheless, 4 animals died of pneumonia and one of meningitis. Drainage of infectious material from the middle ears could also be eliminated as a direct cause of pneumonia inasmuch as only one animal in the group with middle hypothalamic lesions had a middle-ear infection, whereas 4 animals with otitis media* in the other groups did not develop pneumonia. Every precaution was taken to prevent aspiration during tube feeding; in one instance the milk mixture was known to have been aspirated, but this is the only animal in which subsequent microscopic sections of the lungs were positive to neutral fat stains. As a final control on the effects of tube feeding, 7 animals were maintained solely upon intraperitoneal injections of 10 per cent dextrose in Ringer's solution, yet 6 of them died of pneumonia.

Pulmonary emboli. Animals which died of infections that might have given rise to septic emboli were not included in the pneumonia series. Furthermore, the gross appearance of the pneumonic lungs did not suggest multiple septic infarction, but rather showed discrete or confluent bronchopneumonic foci which usually involved all the lobes. This was confirmed by

* The insertion of the Horsley-Clarke ear-cones damaged the middle ear to a certain extent in all experiments.

microscopic examination, which revealed no evidence of emboli or infarctions, but consistently showed intense vascular congestion, alveolar edema and peribronchial pneumonitis. Bacterial smears taken from the fresh specimens showed numerous medium sized, blunt, spore-forming, Gram-positive rods and occasionally large Gram-positive diplococci. Unfortunately, more complete bacteriological studies were not made.

Laryngeal obstruction. All the animals vocalized normally after recovery from the anesthesia, indicating unimpaired laryngeal function.

Gastrointestinal disturbances. Keller (4) has commented upon the importance of constipation in the mortality of his operated animals. Few of our cats were constipated, and when they were, cascara sagrada was given within 36 hours. Postoperative diarrhea occurred in only a few and was not related to the incidence of pneumonia. In no instance was there evidence of infection of the peritoneum or of the gastrointestinal tract.

Exposure to extremes of temperature. None of the animals in this series was subjected to cold- or hot-box experiments. The maximum change of temperature to which any animal might have been exposed was 23°F.; more commonly it was only 17°.

Brain hemorrhage. Keller (4) attributed some of the mortality in his operated animals to hemorrhage in the region of the tuber cinereum. This complication was apparently avoided in our experiments by the use of the Horsley-Clarke instrument, since all extravasations were microscopic and confined to the area of electrocoagulation.

Cardiovascular disturbances. The possibility of progressive failure of cardiovascular or respiratory control as a result of the destruction of hypothalamic centers was not definitely excluded in these experiments, although such failures were not observed either in the recovery animals or in a separate series of experiments in which the hypothalamus of anesthetized animals was serially destroyed by electrolysis while graphic records were made of the respiration and blood pressure (1). Moreover, when 6 animals in our survival group were re-anesthetized and subjected to acute experiments from 7 to 22 days after the original lesions had been placed, none showed an abnormal blood pressure tracing or respiratory curve.

Failure of temperature regulation. Persistent hypothermia occurred in only 7 of the 19 animals with middle hypothalamic lesions, but all pneumonic animals with middle lesions were markedly poikilothermic, *i.e.*, showed a significant fall in body temperature upon removal from the incubator. On the other hand, 3 poikilothermic animals survived from 8 to 18 days and one cat with a caudal lesion had a temperature as low as 97° during 24 hours in the laboratory, yet showed no lung involvement. It was apparent therefore, that disturbances of temperature regulation were important but not determinative factors in the incidence of pneumonia.

Previous observations. The spontaneous and reactive behavior of these animals with rostral and caudal hypothalamic lesions was essentially the same as that described by Teague and Ranson (5) and by Ingram, Barris, and Ranson (6) respectively. The "large rostral" and "large caudal" lesions of Clark, Magoun, and Ranson (7) were somewhat

more extensive rostrocaudally and mediolaterally than ours and probably for that reason were followed by a significantly higher mortality. Also, their incidence of postoperative diarrhea was higher than ours, whereas we observed a considerably greater frequency and degree of fever in response to infection. The high mortality in our animals with middle hypothalamic lesions confirms the observation reported by Beattie, Brow, and Long (8) and by Clark, Magoun, and Ranson (7). The latter authors report a 100 per cent mortality following similarly placed but usually less extensive lesions and state that the " . . . lungs were found congested or consolidated in each case." Nungester and Klepser (9) showed that exposure of rats to cold, presumably lowering their body temperatures, reduced or abolished closure of the glottis during deglutition, thereby permitting aspiration of oral and nasal contents. Whether or not such a dysfunction of the glottis occurred in our poikilothermic cats was not specifically investigated, but that it alone could account for the high incidence of pneumonia is rendered doubtful by the persistence of an active cough reflex and by the precautions taken against aspiration. What relationship, if any, exists between the pneumonia following middle hypothalamic lesions and the "vagus pneumonia" or "neuropathic pulmonary edema" produced by bilateral cervical vagotomy (10–14), or the pulmonary congestion following large doses of eserine (15) is also not determined; however, the work of Schafer (16) indicates that cats can survive bilateral cervical vagotomy provided laryngeal obstruction is avoided. Our cats vocalized normally, indicating undisturbed laryngeal function. Nevertheless, in the 5 animals with the middle hypothalamic lesions which succumbed within 24 hours after operation the marked pulmonary congestion and alveolar edema were strikingly similar to the changes found after double vagotomy.

The severe disturbance in temperature regulation in our animals with middle lesions appears to be definitely related to the high incidence of pneumonia in the group. In this respect, Locke (17) observed that rabbits which were slow to regain their normal body temperature after having been chilled to 95° showed a lower resistance and a higher mortality after the intravenous or intradermal inoculation of pneumococci than did rabbits which regain their normal temperatures rapidly. Similarly, Robertson (18) found it advantageous to lower the temperatures of his dogs in order to facilitate the experimental production of pneumonia by the intrabronchial inoculation of pneumococci. However, a subnormal body temperature could not have been the decisive factor in the mortality rate since less than half our pneumonic animals were hypothermic. Furthermore, 2 animals with subnormal temperatures survived, an observation in accord with the findings of Clark, Magoun, and Ranson (7) who also reported a number of hypothermic cats among their survivals. Neither was poikilothermia itself an absolute factor, inasmuch as 3 of our markedly poikilothermic animals did not develop pneumonia. As stated, therefore, the disturbance of the temperature regulatory mechanism is probably of etiologic importance in the pneumonia which follows middle hypothalamic lesions, but other contributory factors must be sought. In view of the fact that 89 per cent of the animals with middle hypothalamic lesions died of some type of infection whereas the mortality in our two control groups was only 14 per cent, some of these factors may be concerned with a loss of the animal's resistance to sepsis.

This study throws no light upon the problem of precise localization of the neural structures involved in the regulation of body temperature, since only extensive lesions were made. However, our findings confirm those of many other workers (5, 7, 19–32) that the nervous mechanisms which prevent an excessive fall in body temperature lie somewhere between the rostral margin of the tuber cinereum and the caudal borders of the mammillary bodies.

Summary

1. Forty cats were operated upon in 3 series. Bilaterally symmetrical lesions were placed in the rostral (5 cats), middle (26 cats), and caudal (9 cats) regions of the hypothalamus.

2. Characteristic changes in the motor behavior and the emotional responses of the animals are described.

3. All animals with rostral lesions (anterior commissure to optic chiasm) survived. Sixteen of the 19 animals with middle destructions (chiasm into mammillary bodies) succumbed to bilateral bronchopneumonia in 1 to 8 days. Two of the 8 animals with caudal lesions (mammillary bodies and portions of the mesencephalon) died of pneumonia on the 7th day.

4. Animals with rostral lesions retained the ability to prevent an abnormal fall in body temperature; those with caudal lesions showed occasional disturbances of temperature regulation; whereas animals with middle lesions showed marked poikilothermia. All animals responded to infection with fever, but those with middle lesions could not maintain the hyperthermia in the presence of fluctuating environmental temperatures. A close correlation existed between the degree of poikilothermia and the incidence of pneumonia but important exceptions occurred.

5. The following possible contributory factors were studied and found to be of little or no significance in the etiology of pneumonia in the animals with middle hypothalamic lesions: distemper, anesthesia, basilar hemorrhage, peritonitis, aspiration, laryngeal obstruction, pulmonary emboli, gastrointestinal disturbances, and exposure to extremes of temperature. Destruction of the central region of the hypothalamus therefore causes a high incidence of fatal pneumonia in cats, but the specific etiologic factors in this relationship require further investigation.

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PROGRESSION MOVEMENTS ELICITED BY SUBTHALAMIC STIMULATION

WILLIAM H. WALLER

Department of Anatomy, University of South Dakota Medical School, Vermillion

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THE VENTRAL part of the thalamus is generally accredited as a participant in two groups of functions, and two rather ill-defined anatomical subdivisions may accordingly be recognized. Its rostral half, and that part of its caudal half which lies next the midline, are included in the hypothalamus. The lateral part of its caudal half, ventral to the caudal part of the dorsal thalamus, is the territory of the subthalamus. In recent years the hypothalamus has come to be recognized as the seat of a high level of control of autonomic function and many of its activities have been demonstrated, but the functional complexities of the subthalamus have been more difficult to elucidate.

From the nature of its fiber connections (Jakob, 1925; Morgan, 1927, 1928; Papez, 1938) it is evident that the subthalamus is a part of the striatal system, which is, largely on the basis of clinical observations, commonly classed with the motor systems of the brain. Thus far no unequivocal proof, either clinical or experimental, has been adduced to show that any definite motor function is restricted to the corpus striatum, but the results of several recent investigations indicate that motor functions may be demonstrable in the subthalamic part of the striatal system. Since the subthalamus is not sharply delimited anatomically from the hypothalamus, some difficulty in separating the functions of the two parts of the ventral thalamus may be expected. Ectors, Brookens and Gerard (1938) stimulated the cut surface of the brain of the cat exposed by making a parasagittal section and removing about half the brain, and obtained running movements from the region of the ventral thalamus. Masserman (1938) inserted an electrode into the ventral thalamus of the cat with the aid of a Horsley-Clarke stereotaxic instrument, and observed running movements of the front legs during the passage of current to make electrolytic lesions. In the experiments of Rioch and Brenner (1938) stimulation of the rostral part of the hypothalamus was followed, after a long latent period, by violent running movements. None of these investigators determined the neurological localization of the region which was active in initiating the locomotor movements. (See also Hinsey, 1940, which appeared after this paper went to press.)

METHOD

Studies of the results of electrical stimulation of the ventral thalamus were made in 18 cats. Most of the animals were lightly anesthetized with nembutal, the aim being to use the smallest dose that would eliminate practically all spontaneous movement. A dose of about 25 mgm. per kg. was usually sufficient; in some cases a smaller amount was given first, and additions were made until spontaneous movements stopped. In each experiment the calvarium was opened with trephine and rongeurs, the Horsley-Clarke instrument was affixed to the head, and the cat was suspended in a cloth sling hung by six strings from a wood

frame, so that the feet were either free or barely touching the table. A bar across the top of the frame held the carrier of the Horsley-Clarke instrument, which was the sole support of the head.

All stimulation was unipolar. The indifferent electrode was a steel probe inserted handle first into the rectum. The active electrode was a No. 24 nichrome wire coated except at its sharpened tip with insulating varnish and placed at any desired point in the brain by adjusting the position of the needle carrier of the Horsley-Clarke instrument. Alternating 60-cycle current of 6 v. was obtained from the house circuit with a transformer and was passed through a 100 o. radio volume control into the electrode circuit, which was closed and opened with a manual key switch. This apparatus was found to be far superior to the Harvard coil which was tried in several preliminary experiments. Stimulating voltage could be varied by means of the dial on the volume control, which was scaled from 0 to 150, so that, for example, a reading of 25 indicated about 1 v. in the electrode circuit (assuming the resistance of the electrode circuit to be considerably greater than 100 o.). Electrolytic lesions made in some animals, using the same electrodes and current of 2 to 5 mA. derived from a 45-v. battery and controlled by a variable resistor and a 1 to 15 mA. served as obvious marks aginst which the vertical (depth) readings of the needle carrier could be checked.

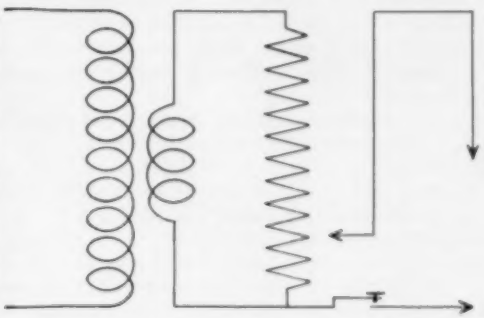

FIG. 1. Wiring diagram of the stimulator.

At the conclusion of each experiment the head of the cat was perfused through the carotid artery with 10 per cent formalin containing 2 per cent glacial acetic acid, and the brain was removed and immersed in the same fluid. After nitrocellulose embedding the brains were cut in 50 μ sections in planes as nearly as possible parallel to the frontal plane of the Horsley-Clarke instrument, and every 8th section was stained with thionin and mounted on a slide. Allowing for 20 per cent shrinkage in the process of dehydration, the sections in the mounted series were 0.5 mm. apart. In some cases parallel sets of Weigert stained sections were prepared. The positions of the needle tracks as seen in the sections were then marked on a set of form drawings of the basal ganglia and compared with the results of stimulation as recorded in the protocols. In each needle track the actual depth of the needle point for each vertical reading was determined by reference to the zero horizontal plane on the form drawings, the position of which was determined in animals in which lesions were made.

RESULTS

In most of the experiments stimulation in the region of Forel's field (Fig. 2, rsb) caused alternating movements of the legs similar to those made by the cat in the normal act of walking. Many variations and inconsistencies were observed, as is common in stimulation work, but only repeatedly recorded responses will be reported.

Localization. The response was localized both topographically and temporally, quite sharply in some animals. Best results were usually obtained when the needle point was 2 to 3 mm. lateral to the midline, 7 to 8 mm. rostral to the zero frontal plane and 3 to 4 mm. below the zero horizontal plane of the Horsley-Clarke instrument. Stimulation of points 1 or 2 mm. dorsal, ventral, medial, lateral or rostral to the point giving the strongest response was entirely ineffective in some cats, but produced results in others if the voltage was increased.

SAMPLE PROTOCOL

Cat. 168. Operated Mar. 31, 1939. Weight 2200 g.; nembutal 15 mgm./kg. (unusually small dose). The distances in mm. rostral to the zero frontal plane (A) and lateral to the midline (L or R) for each needle track are given once at the beginning of the series of records of results observed on stimulation at various distances above (H) and below (H-) the zero horizontal plane in that needle track. Usually several trials at various voltages were made at each vertical setting of the needle. Autonomic responses have been deleted. Voltage is indicated for some points, using the letter P (P10 means 10/150 of 6 v., or 0.4 v.). Responses designated as follows: RF, RH, LF, LH: right front leg, right hind leg, etc.; H: head; R: caudal end of trunk (rear); r or l: moves or turns to right or left; fl: flexion; fo: moves forward; X: walking movements of all 4 legs; XX: running of all four legs; V or VV: walking or running of front legs; sl: slight; C: tegmental response, head and rear to right, trunk to left; ↄ: same, head and rear to left; no: no response. Parts of this protocol have been deleted. The positions of the needle tracks on the right side which are included below are shown in Fig. 2.

10 A.M.: frontal cortex exposed and stimulated.

2 P.M.: stimulation of basal ganglia.

A10R5H5,3:no; H1,O: LF&LHfl;H-2: LF&LH run; H-4:Vl LF better, & LH walks; H-5:LF back RF pawing; H-4 repeated:VV. A10L6H5:no; H3:RF&RHfl; Hl,O:RHfl&HR; H-3:RF&RH pawing; H-4,-5:no.

A10L5H5,3;no; Hl, -1:RF&RHfl; H-3:RF runs; H-4:Hr& lapping.

A4L3 H7,5:no; HO:ↄ&LFfl&RFext; H-1:ↄ; H-2 P10:XX; H-3:X at P10, no at P25; H-4 P25:X; H-5 P15:RF&RH run, chewing and lapping (no LF&LH even at P35).

A4R3 H5,3:no; HO:Hl Rr RFfl; H-2 P10:all run except LH; H-1.5 Pl:XX; H-4 LHfl; H-5 P25:panting, LF runs; H-6 P25: all run except LH, but front legs get in each other's way.

A4R2 H3,2 P20: eyes up; Hl:RFfo; HO P15:RFflLFextRrHl; H-1:same, but runs when current cut to P10 or lower, tail swings in circle; H-2, -3:C; H-4:LF&LHfl.

A4R4 H5,3,1:no; HO, -1, -2 P25:RFflLFextRr; H-3 P5:XX; H-4 P25:LF runs; H-5, -6 P10: all run except LH (unusual result); H-7 P20:V; H-8:LF&LH run.

A8R2 H5,3:no; H2,1,0,-1 P25:C&LFfl; H-2: same and runs after current off; H-3 P10:X if started at P20 or if front leg is given a push; H-4 P10:X but stops while current is still flowing.

A11L9H5,3,1,0,-1,-2,-3:no; H-4: chewing.

A4L1 Eye movements and tegmental response, no walking. Further cortical stimulation and small lesion made in right motor cortex. Incision closed; cat returned to cage. Second operation April 26, 1939.

A8L4 H5,3:no; H1,2:RFfl; H-1:no; H-2,-3:RFsl fo Hr; H-4,-5: lapping, panting.

A8L2 H5,3:no; H2,1,0;RFfl; H-1:no; H-2,-3,-4:RFfoHr; H-5: lapping.

A8R2 H5,3,1:no; HO,-1 P17:V; H-2:C; H-3 P10:V; H-4 P13:V; H-5 P24:V; H-6 P30: irregular jerk.

A8L1 H5,3,2,1:no; HO,-1:RFfl; H-2:ↄ&RFfoLFext; H-3 P10:VrHr; H-4: same at P17; H-5,-6:no.

A8R1 H5,3,2,1,0,-1,-2,-3:no; H-4 P35-VV; H-5 irregular jerk; H-3 P35:VV.

A8R3 H5:no; H3:very sl V; H2:trunk left; H1,0:LFsl fl; H-1,-2 P14:VlHl; H-3 P13:X; H-4 P16:V; H-5 P29:V.

A8L3 H1; RFfl; HO:no; H-1:sl X; H-2:X; H-3:RFfo; H-2:no; H-1: sl V; HO:RFfl.

A10R7H5,1,3:no; H2:LHfl; HO P15:X continues after current off; H-1:LHfl; H-2,-3,-4:no; replaced needle because of damaged insulation.

A10L7H5:Hr; H3,1,0:no; H-1,-2:RHflHr; H-3,-4,-5,-6:no.

A10L9H5,3,1,0,-1,-2,-3,-4,-5,-6,-7,-8:no; same at A10R9:no.

A9R6 H5,3,1,0,-1:no; H-2:LHfl; H-3:LFsl fl; H-4,-5,-6,-7:no.

A8R2 H-4 P15:V;H-5 P50:V; H-3 P17:V.

A9L5 H5,3,1,0:no; H-1 P18:V; H-2,-3,-4:RHflHr; H-1:RF&RHfl; HO P15:V.

Several punctures were made in the midbrain (A4) and walking responses were obtained from both sides.

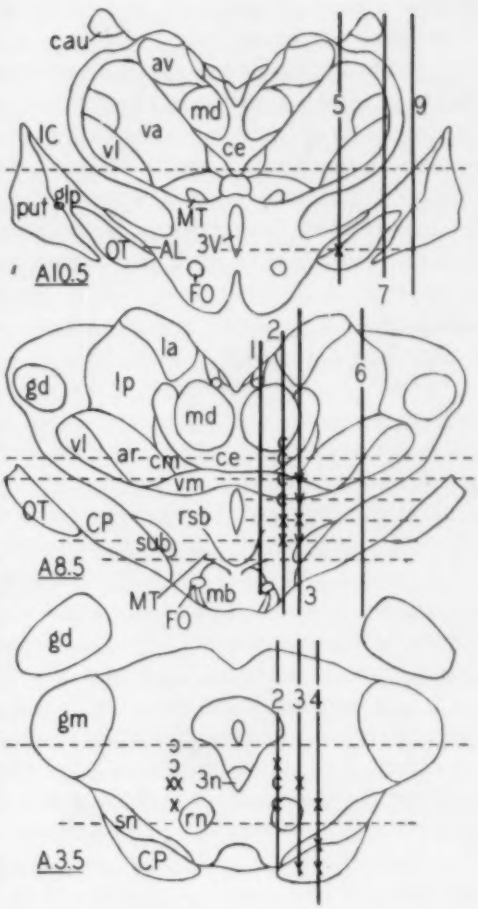

FIG. 2. Outline drawings of sections through the rostral (A10.5), middle (A8.5) and extreme caudal (A3.5) parts of the thalamus, 3 times natural size. Some of the needle tracks made in one animal, and responses obtained at points along them, are marked on the right side (see sample protocol). Needle tracks at A8 and A9 are marked on the drawing at A8.5. The number beside each needle track gives its distance from the midline in mm. The zero horizontal plane (HO) and a plane 4 mm. below it (H-4) are marked by interrupted lines on each drawing, and in addition, planes 1, 2, 3 and 5 mm. below the zero plane are shown at A8.5. Points at which progression movements were obtained are marked X if all four legs were involved, V if only the front legs moved. Points at which the tegmental response was elicited are marked by a C if the trunk was bent so as to be concave to the right, by a reversed C if the convexity was to the right. Labels: AL, ansa lenticularis; cau, caudate nucleus; CP, cerebral peduncle; FO, fornix; glp, globus pallidus; IC, internal capsule; mb, mammillary body; MT, mammillo-thalamic tract; OT, optic tract; put, putamen; rn, red nucleus; rsb, reticular subthalamic nucleus of Forel's field; sn, substantia nigra; sub, subthalamic nucleus of Luys; 3V, third ventricle; 3n, oculomotor nucleus: Nuclei of the dorsal thalamus: av, anteroventral; ce, central; cm, centrum medianum; gd, lateral geniculate body; gm, medial geniculate body; la, lateral anterior; lp, lateral posterior; md, medial; va, ventral anterior; vl, ventrolateral; ar, arcuate; vm, ventromedial.

Nature of the response. Rhythmic movements of the legs began within 2 or 3 sec. after the stimulating circuit was closed. They were ordinarily smoothly executed from the start, but occasionally there was a brief period of confusion before the regular alternation was established. Frequently the first steps were small ones, but as the current continued to flow the amplitude of the excursions of the legs increased to maximum in the course of 5 to 10 sec. When the response was confused or submaximal at its beginning it was usually apparent that the homolateral forelimb was responding best and was setting the pace. Once the maximal response was in progress, well coordinated walking movements could be kept going for more than a minute by continual stimulation, but no attempt was made to determine the upper limit of duration of effective stimulation. When the stimulus was stopped the movements ordinarily ceased promptly, but if the anesthetic was unusually light they continued several seconds longer. The excursions of the front legs were often in a plane oblique to the longitudinal axis of the body,

so that if the cat had been free he would have progressed forward and away from the stimulated side.

Incomplete responses. In some cases the hindlegs responded with movements of lesser amplitude than those of the forelegs, or did not move at all. Attempts to demonstrate the existence of separate points from which "two-legged" and "four-legged" walking could be obtained were unsuccessful. When only the front legs moved it was often apparent that the amplitude of the excursions was greater homolaterally than contralaterally. At times walking movements were performed by three legs while the activity of the contralateral hindleg was almost imperceptible. Three-legged walking in which the homolateral hindleg lagged was elicited also, especially by stimulation near the cerebral peduncle.

Effect of voltage variation. To elicit locomotor movements from the point of best response it was in most cases essential that the stimulus be neither too weak nor too strong. The rate and amplitude of the movements could not be controlled by changing the voltage, since supra-threshold stimuli evoked the tegmental response (see below) or irregular jerking movements. The voltage requirement varied in different cats from 2 to 15 on the volume control dial (0.1 to 0.6 v.). In those animals in which the progression response was not sharply localized and could be produced by stimulating points 1 mm. or more removed from the focal point in the subthalamus, effective stimulation at such points was in the range from 12 to 35 on the dial (0.5 to 1.4 v.), somewhat less precision in voltage regulation was required, and the movements were slower than those elicited by stimulation at the focal point.

Effect of depth of anesthesia. Accuracy was hardly less important in administering the anesthetic than it was in regulating the stimulating voltage. If the anesthesia was too profound no walking movements could be elicited. If it was too light, spontaneous movements interfered with observation of stimulation and the cat continued to move its legs after the stimulating current was stopped. Poor localization seemed to be associated with unduly light anesthesia. The locomotor movements obtained by stimulation at the point of best response were rapid in some animals; the legs moved more slowly, and sometimes rather stiffly, in cases in which the anesthesia was slightly deeper.

Stimulation of other regions. Walking movements were elicited in some animals by stimulation of a region extending caudally from the point of best response. The levels from A5 to A7 (not illustrated) have not been completely studied, but at A6 the locomotor zone seemed to be slightly more ventral and nearer the midline than it was at A8. At A4 it was found in the tegmentum dorsolateral to the red nucleus. Locomotor responses were occasionally obtained from the region of the ansa lenticularis and at times from the globus pallidus and putamen, but these were inconsistent. Walking movements could be elicited by stimulation of the internal capsule and cerebral peduncle by using voltages greater than those required to obtain the subthalamic response. Capsular progression movements differed from the sub-

thalamic response in that they were characterized by a tendency of the homolateral limbs, especially the hindleg, to lag behind.

Single limb movements. With the needle point in the subthalamus 1 or 2 mm. from the point at which locomotor movements could best be obtained, the response to minimal stimulation frequently was a single caudally directed movement of the homolateral forelimb. This response also occurred at times with the needle in the locomotor region, if the voltage was slightly too low for progression. Stimulation in the dorsal part of Forel's field (A8L or R3H-1 or -2) occasionally evoked flexion of the homolateral foreleg. The response of the ventral nucleus of the dorsal thalamus was flexion of the contralateral fore- or hind-leg, executed more deliberately than the contralateral flexion seen on stimulation of the internal capsule or cerebral peduncle.

Tegmental response. Stimulation near the red nucleus commonly evoked the tegmental response as described by Hinsey, Ranson and Dixon (1930), which consisted of bending of the rostral and caudal parts of the body toward the stimulated side. Curvature of the trunk was maintained for the duration of the stimulus, but some of the various limb movements which accompanied the response were rhythmic or clonic. In the subthalamus the region immediately dorsal to the locomotor point often gave the tegmental response. At times rhythmic pawing movements of the legs were superimposed upon the tegmental posture and it was difficult to separate the two responses. Slight reduction in voltage seemed to be the best procedure to eliminate the tegmental posture and produce uncomplicated progression movements. At certain points, particularly near the cerebral peduncle at A4, bending of the rostral and caudal parts of the body away from the stimulated side was occasionally seen (see Mettler *et al.*, 1939).

Autonomic responses. Since the locomotor point in the subthalamus is immediately adjacent to the hypothalamus it is not surprising that autonomic responses were often observed (Ranson and Magoun, 1939). Pupillary dilation commonly accompanied the walking response. No attempt was made to correlate the records and localize the regions from which autonomic responses were elicited.

Discussion

The promptness, smoothness and regularity of the locomotor movements produced by subthalamic stimulation are evidence in themselves that the subthalamus contains a specific mechanism which governs the alternation of the legs in walking. It is hardly possible that the effect observed was caused by spread of current to pyramidal or other neighboring structures, since (i) the response was weakened or abolished by misplacement of the electrode in any direction except caudally, (ii) the strongest responses to subthalamic stimulation were homolateral, and (iii) the walking response was obtained in the subthalamus with stimulation of lesser strength than was needed to elicit rhythmic alternation from the internal capsule. Probably the activa-

tion of progression movements which can be produced by stimulation of the cerebral cortex or cortical fibers in the internal capsule (Tower, 1936) is effected through direct or indirect connections to the subthalamus. Attempts to verify Wilson's (1924) observation of walking movements on stimulation of the dorsal thalamus were uniformly unsuccessful. Except for contralateral limb retraction and turning of the head and eyes to the side opposite that stimulated, no somatic movements were consistently obtained by dorsal thalamic stimulation.

The locomotor point appears to be in Forel's field at the level of the subthalamic decussation, dorsal to the mammillary body and near the subthalamic nucleus of Luys. Hinsey, Ranson and McNattin (1930) found that cats in which this region had been separated from the more caudal parts of the brain stem by transverse section were unable to walk, while others with transections rostral to the mammillary bodies were not so disabled. The principal neurological relationship of the subthalamus is its reciprocal fiber connection to the corpus striatum, and occasional observation of walking movements in response to striatal stimulation indicates that the globus pallidus may normally activate the locomotor center in the subthalamus. But since experimental destruction of the corpus striatum (Morgan, 1927) does not incapacitate an animal for walking, the essential center must be in the subthalamus.

From the results thus far obtained, it seems reasonable to conclude that the subthalamus directs the order of movement of the limbs in walking by impulses which descend through the tegmentum dorsolateral to the red nucleus. That some mechanism other than the pyramidal and rubral systems must be capable of managing the act of progression was demonstrated by Evans and Ingram (1939), who found that a cat with lesions of its pyramidal tracts and red nuclei regained the ability to walk after a short period of disability. The nature and localization of the response to subthalamic stimulation seem to show that, at least in the cat, the descending tract from the subthalamus plays the leading role in regulating the alternation of the limbs. Since the feet were hanging free, there was, however, no evidence that the subthalamus has any direct control of the mechanisms responsible for bearing the body weight. Although under the conditions of the present experiments the reflex arcs normally activated by contact of the footpads were not in use, it is probably true that in directing the order of movements the flow of impulses from the subthalamus was materially assisted by crossed extensor and other spinal reflexes.

Since the depth of anesthesia affected both the degree of localization and the rate of execution of the response, it is quite probable that further variations may be found when the effects of subthalamic stimulation are investigated under different anesthetics.

Summary

In cats anesthetized with nembutal, alternating movements of the legs

similar to those of normal walking and running were elicited by 60-cycle alternating current stimulation of the subthalamus in the region dorsal to the mammillary body. The sharp localization and low threshold of the response indicate that the subthalamus contains a specific center which directs the order of movement of the legs in locomotion.

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ELECTRICAL ACTIVITY OF THE LATERAL GENICULATE OF CATS FOLLOWING OPTIC NERVE STIMULI*

GEORGE H. BISHOP AND JAMES S. O'LEARY
WITH THE ASSISTANCE OF C. B. MUELLER IN ANALYSIS OF RECORDS.
Laboratory of Neurophysiology and Department of Anatomy, School of Medicine, Washington University, Saint Louis, Missouri.

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TO ASCERTAIN the relation of the form of stimulus arriving over the visual pathway to the resultant cortical activity, we have recorded by means of the oscillograph responses from the vicinity of the dorsal nucleus of the lateral geniculate body in the cat. In order to locate the sources of such responses, all experiments have been controlled histologically, that is, the paths of all needle electrodes have been traced in serial sections 20 mm. thick. At critical depths of insertion, with needles insulated to within 0.5 or 1 mm. from the points, electrolysis at 1 mA. for a minute or less has served to identify the structures led from.

Responses were initiated by single or repeated condenser shocks or brief galvanic currents delivered through a rotating interruptor to the optic nerve. Nembutal, dial, ether, and magnesium sulphate were used as anaesthetics, the animals being usually maintained at a level where a single maximal shock caused no protest, but shocks repeated at 1 per sec. intervals aroused the animals (presumably by stimulation of pain fibers in ciliary nerves). During the preparatory operation ether was administered by tracheal cannula. A suitable level is maintained for experiment by, for instance, 0.2 to 0.4 cc. nembutal per kg., when 0.5 to 0.7 is required for a surgical anaesthetic in cats. Operations involved two procedures: first, removal of the eye and its muscles, without destroying the blood supply of the optic nerve by too clean dissection, a successful preparation being considered one in which a stimulus of 0.1 to 0.3 v applied for 0.5 msec. induced a threshold response; and second, exposure of the opposite cortex, with removal of its lateral aspect in some cases to expose the geniculate. If the retinal vessels of the strip of tissue left as a handle to the nerve cease bleeding, the nerve threshold rises promptly and the nerve soon ceases to respond at all. Apparently the venous return is destroyed in this operation. Needle electrodes may be employed to stimulate the nerve without removal of the eye, but with less precise control of response. Removal of the cortex damages the geniculate, probably through interfering with its circulation, to the extent that facilitation by the first of two shocks at the geniculate level had not been observed in such preparations. Needles thrust through the ectosylvian cortex into the geniculate region obviate the necessity of cortical operation.

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Responses of Optic Nerve, Optic Radiation, and Cortex to Optic Nerve Stimulation

It has been shown previously in the rabbit (Bishop, 1933b) that the optic nerve response to a maximal electrical stimulus includes two potential spikes, with indication of a third slower wave. It has also been stated that the fibers involved in producing the first of these spikes, that is, the group of larger diameter, were the only ones which activated the cortex (Bishop and O'Leary, 1938), and that fibers of the second group passed without synapse toward the colliculus. Allowing for some degree of overlap of these two size groups, this finding is confirmed in the cat. Further, the third smaller wave just behind the second in conduction rate can often be picked up, and a fourth, slow and temporally dispersed, is unmistakably present in favorable leads. (Fig. 1.) Second, third, and fourth groups of fibers can be traced past the geniculate. The second is followed by a prominent response from the pretectal and adjacent regions, the fourth causing a large response from the colliculus. The thresholds of these fibers correspond roughly to their conduction rates, the fourth group having the approximate rates of C fibers in peripheral nerves. (A much more prominent wave appears in this relative position in the frog optic nerve record, Bishop, *l. c*)

In assigning potentials to structures, consideration must be taken of the fact that active tissue embedded in the (relatively) inactive mass of the brain will induce flows of current, and therefore potential differences, at some distance from the source. Some of the criteria for analyzing records of such diffused potentials have been discussed (Bartley, O'Leary and Bishop, 1937), and the conclusions arrived at below concerning the responses of specific structures are our best inferences based on what principles we can set up. That our principles are at present inadequate is evident from the circumstance that we cannot interpret some of our records, in which cases we can only fall back on the assumption, not conclusively established, that activity in any nervous tissue is accompanied by relative negativity of the active region. Aside from general physical considerations, chief reliance can be placed upon the assumptions that, *other things being equal*, the closer the one of two electrodes is to an active tissue, the higher will be the potential recorded from that tissue; that as an electrode is pushed through or past an active structure the most abrupt changes in the potential will occur just as the electrode passes through a plane containing the structure in question and the other electrode; and that if the electrode strikes and injures active tissue, it may serve as a dead-end lead, with consequent relative positivity of its immediate vicinity. The all too prevalent difficulty is that other things are not always equal.

Facilitation. It is certain that to one volley of impulses in the optic tract, the radiation responds with a single volley. To a threshold volley, a response of the radiation cannot be recorded. With increase of strength of single stimuli, the response of the radiation builds up more rapidly than does the response of the tract, *above the threshold* for *radiation response*. The second of

FIG. 1

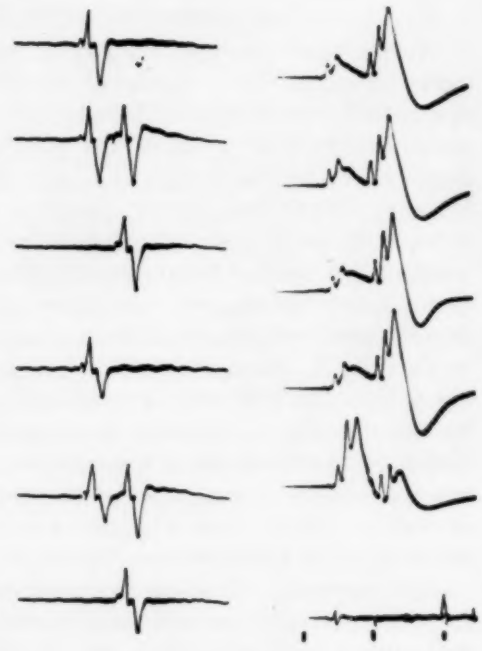

FIG. 2

FIG. 1. Potentials assignable to optic tract. Left, first 3 records, strengths of DC stimulus in ratio of 1:4:15. Dots below indicate the four waves, an extra spike in the third record X being a repetitive first spike. Time 5 msec. Leads from needle electrodes in tract near geniculate and in wall of ventricle. Right, slow waves following radiation response, leads from dorsal nucleus to wall of ventricle. The first tract spike and radiation spike are included in the highest deflection (dot), the slightly lower slow wave extending from its falling phase indicating negativity at the cell region. Time below 5 msec. intervals. Left, lower, first spike of tract up, radiation spike triphasic. The second tract wave (below) appears just behind and overlapping the radiation spike. Right, slower records at stimulus strengths of records to left. Compare the triphasic form of the radiation spike with the diaphasic form of the slow potential. The triphasic form is the result of the impulse travelling *past* one electrode. The implication is that the slow wave does not propagate. Time 5 msec. intervals.

FIG. 2. Cat, light nembutal anaesthesia. Left column, leads from tract to radiation, the first, paired, and second responses; 2.5 msec. interval between members of pair; upper series of 3, each record after a rest interval of at least 5 sec. Lower 3, each record one of a series repeated at 1 per sec. The initial or tract spikes are all equal. The radiation spikes are all lower in the repetitive series, except for the second of paired responses. This has the amplitude of single responses, while in the upper series, the second of the pair is even higher than any single response. All stimuli above maximal for first tract spike. Note summation of positive after-potentials in paired records. Right column, read from bottom up. Leads radiation to surface of lateral gyrus of cortex, 3 msec. intervals between pairs of shocks, first 5 pairs of a series, at intervals of 1 per sec. In first responses of each pair, radiation spike decreases after first record, but cortical response decreases much more, the later responses more than the earlier. In second responses of pairs, radiation spike of first record is higher than in first response, and remains so in subsequent records. Records after the first show marked facilitation, especially of diphasic slow wave. Increase of stimulus strength did not alter this picture, but increase of interval between shocks of pair did. Time 5 msec. intervals.

two stimuli properly timed, both being "maximal" for the tract, may induce a larger response of the radiation than any single stimulus, and also below maximal, the second of two stimuli is considerably more effective than one alone. (Fig. 2A). All these findings indicate that facilitation in the sense of spatial and temporal summation is operative even with "maximal" stimuli, and are consistent with the notion that more than one impulse in one fiber is required to fire a synapse. They are not consistent with the notion of a one-to-one single fiber pathway from retina to cortex, inferred conventionally from data on sensory discrimination and degeneration experiments, but they are consistent with such a theory as that of "partially shifted overlapping," as proposed by Lorente de Nó (1934). Marshall and Talbot (1940) report similar findings.

The optic radiation also shows one type of variation in response to slowly repeated stimuli similar to that exhibited by the optic cortex, and in part responsible for the latter. With nerve stimuli at one second intervals, the second and following responses are equal, and definitely lower than the first, under the degree of anaesthesia employed. At five second intervals all responses are identical at the geniculate level (with further variation at the cortical level, see below). This phenomenon is more obvious when paired stimuli are repeated at 1 and 5 second intervals. With maximal paired stimuli at five second intervals, the second response of each pair is slightly but definitely higher than the first, with the appropriate interval up to 15 msec. between shocks of a pair. At one second intervals, the second and following pairs show a much decreased first response and a full-sized second response, which may be greater than an isolated response. That is, facilitation due to the conditioning response more than overcomes the depression due to the two responses occurring a second earlier. The same thing occurs with submaximal stimulation, with the added complication that weak stimuli may be complicated by depression of the optic nerve at the site of stimulation following the conditioning shock, presumably assignable to impaired circulation at the eye socket.

In responses recorded from two electrodes, one in the optic radiation and one in the cortex, similar phenomena indicating facilitation may be recognized in the cortex. Taking into account the amplitude of radiation spikes, facilitation of the second of a pair of responses may then appear in the cortical spikes following the radiation spike. (Fig. 2B.) The situation is more complicated for two reasons. First, the type of facilitation exhibited at the geniculate synapse also occurs at each cortical synapse, that is, the effect is cumulative during the course of the cortical sequence. One cannot say that facilitation at a given cortical synapse is any greater than that occurring at the geniculate level. Second, the amplitude of cortical responses varies independently of the size of the geniculate response. One factor involved in this variation is the phase of the spontaneous alpha rhythm at which the stimulus falls, the larger responses occurring when the stimulus is applied during the surface-positive phase (Bishop, 1933a). This effect is superposed on the

type of facilitation in the geniculate; at one second intervals, responses after the first are on the average lower than single or first responses, and the cumulative difference appears to be greater than in the case of the geniculate alone. At 3 to 5 second intervals, varying from animal to animal, recovery is complete (see also Marshall and Talbot, *l. c.*).

In animals exhibiting a marked variation in amplitude of cortical responses to stimuli at 1 per sec., a slight change of frequency may result in a fluctuation no longer random, and a slow waxing and waning occurs. This frequency is apparently one which is a simple multiple of the alpha rhythm, as can be demonstrated more positively in the rabbit (Bartley, 1936), where the alpha rhythm is usually more regular than in the cat. In the cat we have not been able to maintain such synchronism for more than a few coincidences or beats.

Aside from such effects, results of paired stimuli indicate that each successive synapse level of the cortex is susceptible to facilitation like that at the geniculate level, although we cannot correlate, in the more complicated records from that region, a facilitating effect with a slow potential of the character of the after-potential of nerve.

Homolateral responses to optic nerve stimulation. Of the three cell layers of the geniculate of the cat, degeneration experiments indicate that the middle layer receives the uncrossed optic nerve fibers (Minkowski, 1913). We have led from the geniculate of one side, while stimulating both optic nerves with single shocks, to determine whether any phenomena of interference or facilitation appeared that would suggest fusion of images at the geniculate level. (Fig. 3.) So far, no such evidence has been obtained. The relative magnitudes of response from stimuli to the two nerves have varied in different preparations from almost no homolateral response (10 or 15 per cent of the contralateral) to nearly equal responses (70 per cent). Responses from the cortex roughly parallel those from the geniculate in this respect in each preparation. In rabbits, the homolateral response of the cortex is always relatively smaller than in most cats; in 3 of 6 monkeys, in which records were taken from both optic areas, the responses from the two were approximately equal. (Fig. 3B.) Our results would indicate that cats are variable with respect to the homolateral projection of the retina on the cortex, and that facilitation between impulses from the two sides is relatively slight. Marshall and Talbot (*l. c.*) report facilitation at the cortical level but not at the geniculate.

Localized potentials. "Slow" potentials are also recorded from the cell regions of the geniculate. (Fig. 1 and 6.) No corresponding potentials are recorded from either tract or radiation, except that leads in the injured radiation, near a cut surface, may show after-potentials of considerable amplitude. Such injury potentials, which look like positive after-potentials, may appear immediately after a needle has been placed in the radiation, and decrease rapidly to disappear within a few minutes. (Fig. 3A.) They are probably a result of injury. The slow potentials of the normal tract or radiation are too low to be detected above the "noise" level of the region. In con-

trast to these, the slow potentials recorded from the vicinity of cells are specifically diphasic, follow the radiation spike rather than the tract spike, and the first phase has the same polarity as the spike which apparently initiates it. They are reminiscent of the slow processes observed by Gasser and Graham (1933) in the spinal cord, interpreted by them as the responses of intercalary neurones. The first or "negative" phase is also similar to the slow potential observed by Lorente de Nó (1939) in the oculomotor nucleus, interpreted by him as a slow depolarization of the spike negativity process of the cell body. We are inclined to the latter interpretation of our findings, especially since no intercalary neurones are present to which the process might be assigned. Further, the negative phase has the dimensions of the facilitation appearing after a first response.

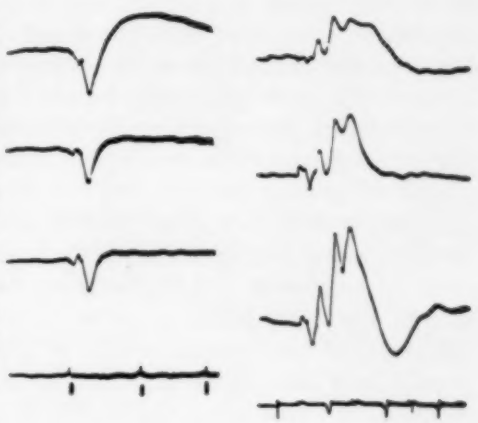

FIG. 3. Left column, 3 responses at 1 min. intervals, the first immediately after inserting an electrode into the radiation. First, faint spike, tract wave; second, radiation, followed by a positive after-potential, the latter progressively decreasing. When the cortex is removed, leads from near the cut surface of the radiation show similar potentials that are more persistent. Time 5 msec. Right column, cortex responses, lateral gyrus surface to radiation; upper, homo lateral nerve stimulated, middle, contralateral, lower, both simultaneously with maximal shocks. The two upper records add up to the lower, showing no facilitation, except for the final wave below the base line. Time 5 msec. intervals.

This potential might be interpreted as similar to the negative after-potential of nerve fibers, but is relatively much greater in amplitude. The slow potentials of two responses are summated, and the contribution of the second may be greater than that of the first. Therefore, we judge this slow potential to arise from cells or their dendrites in the geniculate nucleus, rather than from the fibers of tract or radiation, and to represent the sequella of the main response, rather than the immediate process of conduction which precedes it.*

* This is not a necessary conclusion. The records can obviously be interpreted either as those of a spike followed immediately by a slow wave (slow depolarization of the spike process), or as of a spike *superposed upon* a slow process in the record (spike and slow process in different structures, say, axons and dendrites or cell bodies). The presence at the same region of different structures to which these processes might be assigned renders a separation by differential leads impossible here, and any theoretical interpretation is compromised by the assumptions one must make to account for potentials being led from such structures as cell bodies or dendrites at all. To account for such long-lasting potentials one must assume either slower conduction than is reasonable in this case (synapse time 0.5 msec.), or localized differences in the degree of depolarization in different regions of the structure, persisting throughout the slow record. Assuming, for instance, that one end of the cell body, say the axon hillock, becomes more strongly negative than the rest, there seems to be

Repetitive responses of cerebral cortex. From the facts that the size of the cortical response varies, depending on the phase of the spontaneous alpha rhythm in which it occurs, and that as strychnine abolishes the spontaneous rhythm, it leaves the specific response higher than normal and less variable, we have inferred (Bishop, 1935) that optic nerve impulses at a frequency above that of the alpha rhythm would be relatively ineffective in exciting a given cortical pathway at more than about 6 per sec. (in the cat). This is a particularly significant factor since single volleys may set up not only the immediate cortical response, but also a train of alpha waves, which should then control the effectiveness of succeeding volleys. "Continuous" vision could then be assigned to successive activation of parallel pathways.

This interpretation requires modification in the light of the present work. In the first place, the facilitation described above acts to oppose the phasic depression connected with the alpha rhythm, if the frequency is sufficiently high. In the second place, anaesthesia not only decreases such facilitation, but greatly accentuates the depression of responses initiated during the surface-negative phases of the alpha waves. Thus the degree of anaesthesia employed in our previous experiments was a material factor in the results. The phasic depression is, however, not abolished in rabbits which have practically recovered from ether (Bishop and O'Leary, 1938), with wounds locally anaesthetized. Further, Heinbecker and Bartley (1940) have found the same cycle of depression and facilitation after a first volley to the saphenous nerve of cats, recording from the sensory-motor cortex under local anaesthesia and tetramethyl ammonium iodide. In these cases the second responses are depressed but not abolished, which must mean that some cortical elements are blocked, but not all of them. The sequence then appears to be as follows: depression in the relatively refractory phase of a first response; facilitation for a few thousandths of a second; depression during the surface-negative phase of the alpha wave set up by the first stimulus, and facilitation during the surface-positive phase, etc.

Records were taken from the optic cortex of cats with minimal anaesthesia, at various frequencies, by photographing a succession of lines across the oscillograph on a moving strip of paper. (Fig. 4.) Apparently the first volley sets up a complete cortical response, while successive volleys are lower, the later elements of each response being the more readily depressed. However, at about one-sixth second intervals there is an increase in amplitude of response, which at the frequency employed is grossly noticeable as a wider separation between successive lines of the record, followed by a crowding together. This results from the fact that each response serves as the base line

no objection to interpreting the spike as that of the axon itself, and assigning to the cell body only a low long-lasting potential. Such an inference would possess the virtue of accounting for repetitive responses to single or summated impulses on a relatively simple structural basis. It is compromised by the fact that such repetitive responses are normally found only where extreme structural complexity exists, and not, for instance, in the dorsal nucleus of the lateral geniculate. See Lorente de Nó (1939), Heinbecker (1932), and Renshaw, Forbes and Morrison (1940).

for the next, and summation or overlapping takes place. After a few cycles, all responses are approximately equal.

The events may be explained as follows. The first response sets up an alpha cycle, the depressive phase of which counteracts the facilitation that successive volleys might otherwise exhibit. The alpha cycles of the following volleys apparently do not develop, and the first alpha cycle controls the amplitudes of following responses, resulting in a second maximum one-sixth second after the start. During this maximum a second alpha cycle can be set up, but the fact that several shocks are delivered during this part of the cycle results in temporal staggering of alpha processes. For this reason the bursts at one-sixth second intervals do not persist, but soon average out, that is, the alpha responses in different elements become scattered and temporally dispersed to an average steady state. We have no conclusive evidence that alpha cycles are still present in each unit after they are no longer manifest in the summated record, but we infer their existence from the fact that if the cortex is stimulated only at one-sixth second intervals, or multiples of this, each response may be full height.

In normal vision this same chain of events should occur, but with much greater dispersion, due to the lack of initial synchronization of optic nerve impulses from the retina.

Destination of Size-Groups of Tract Fibers

Histologically, properly directed sections through the optic tract, stained by Davenport's (1939) silver technique, show segregation of fibers according to size (Gudden, 1886), as indicated by potential records. The main bundle of optic tract fibers bends sharply medial to pass under the

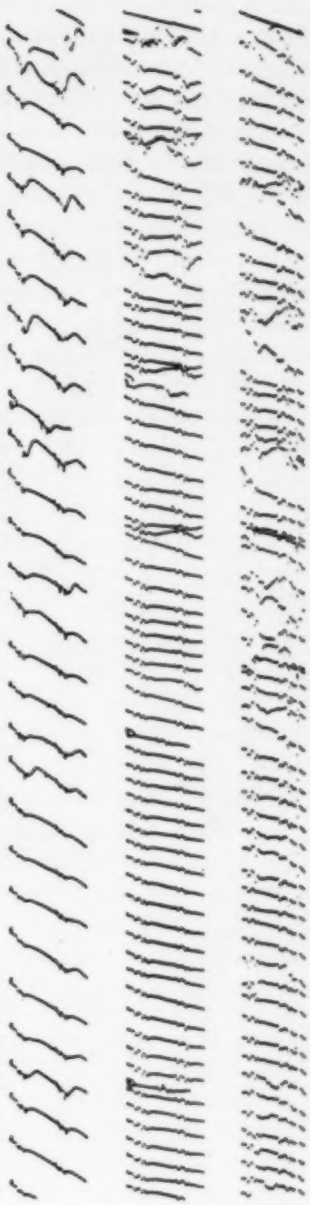

Fig. 4. Stimulation of optic nerve, leads from contralateral cortex, at rates of 40, 80 and 100 per sec., all supramaximal. Successive sweeps photographed on moving paper strip, two responses to each sweep, 20, 40, and 50 sweeps per sec. The time can thus be estimated from the sweep frequency, as 50, 25, and 20 msec. respectively for one sweep. Increases in amplitude of responses, and changed spacing in lines due to summation of successive responses occur at about one-sixth second intervals after the first stimulus, or with the frequency of the alpha rhythm. Further analysis in text.

geniculate proper at the lower apex of the ventral nucleus. A sheet of the remaining fibers leaves here to invest the ventral nucleus, especially its medial and posterior surfaces, and envelops the ventral and posterior surfaces of the dorsal nucleus, supplying fibers to these surfaces. Radiation fibers leave the lateral and anterior surfaces of the nucleus, which is arranged as a three-layered sheet bent into a S-shape (Rioch, 1929), the posterior limb of the S somewhat dorsal to the anterior. The posterior limb broadens out to form a hemispherical cap for the radiation; the anterior limb forms a similar cap for the division of the tract going to it. The medial curvature of the dorsal nucleus is continuous with the posterior portion of the pulvinar (Rioch, *l. c*), and the tract to the colliculus runs below this, coming close to the surface posterior and medial to the groove between medial and lateral geniculate. (Fig. 5.)

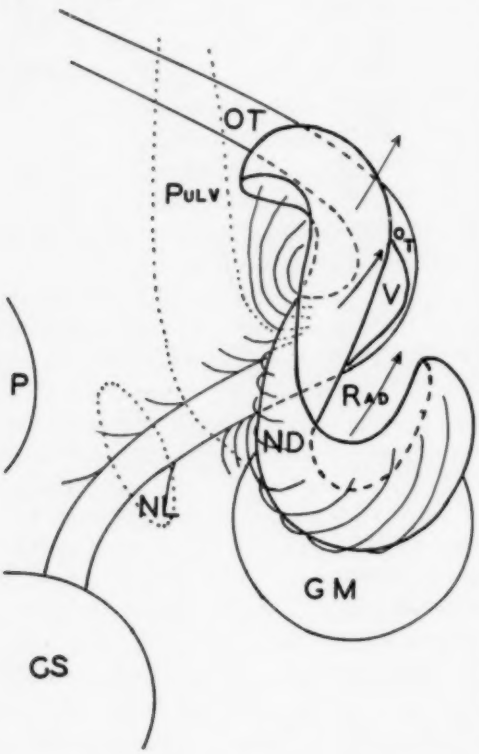

FIG. 5. A schematic diagram, not to scale, to indicate relations of optic tract to adjacent regions of the thalamus, as inferred from electrical records. Based on reconstructions from 20μ Nissl-stained sections, 0.36 mm. apart, normal cats; and a Marchi degeneration series after removal of one eye. Some fibers may also pass over the dorso-posterior surface of the geniculate and across the pulvinar to the pretectal region, as inferred by Barris, Ingram and Ranson. The whole region lying between pretectal area, superior colliculus and geniculate is traversed by optic tract fibers lying close to the surface. Synapse stations appear not to be confined to the specific nuclei usually assigned a visual function. Taking the dorsal nucleus as one limit of the distribution of optic tract fibers, and the superior colliculus as the other, the larger fibers distribute in general, but not exclusively, to the anterior regions and the smaller to the posterior, as indicated by post-ganglionic responses to shocks of different strength which are shown to activate fibers of different sizes. *OT*, optic tract. *ND*, nucleus dorsalis of lateral geniculate. *V*, nucleus ventralis. *GM*, medial geniculate. *Rad.*, optic radiation. *Pulv.*, pulvinar. *NL*, nucleus lentiformis mesencephali. *CS*, superior colliculus. *P*, pretectal area.

The division of the tract passing to the geniculate, and entering its cell layers, contains most of the largest fibers of the nerve, and some medium sized. Passing with this bundle, however, are some of the smallest fibers of the nerve. We have been able to recognize no responses from these small fibers in the geniculate, nor to detect any secondary effect of their stimulation in the optic radiation or cortex, which may indicate only that our technique is not sufficiently discriminating.† The remaining tract contains me-

† A tract second spike and its post-ganglionic response can be recorded from the re-

dium sized fibers and many more fine fibers than appear in the tract to the dorsal nucleus. It is not clear which, or how many, of these fine fibers are the fine branches of coarser geniculate fibers recognized by Barris, Ingram and Ranson (1935), but most of those to the colliculus, and many of those to the dorsal nucleus, obviously come from the optic tract and nerve, and as suggested by a corresponding slow potential in the frog optic, presumably arise in the retina.

Records from various regions of the optic tract distribution (Fig. 6.) indicate that in general the smaller fibers pass further posterior, toward the colliculus, before they synapse than the medium-sized, while the larger fibers pass a shorter distance, to the geniculate. Between these two bodies lie various structures which have been inferred to receive optic tract fibers, such as pulvinar, nucleus lentiformis mesencephali, and pretectal area. Employing as criterion not only a record of the second tract wave, but a post-ganglionic wave which follows this, and which does not follow weaker stimuli that excite the first tract wave, we have traced such fibers to some of these structures and also to the marginal territory along the tract bordering the medial geniculate nucleus, and to the territory just medial and anterior to the dorsal nucleus of the lateral geniculate. These post-ganglionic responses are very well localized, and movement of the critical electrode half a millimeter in the vertical plane may determine their presence or virtual absence in the record. Pending further work now in progress, at present the following scheme of optic tract fiber distribution emerges.

The main bundle, from the region ventral to the ventral nucleus of the lateral geniculate, to the superior colliculus, loses fibers continuously, the contribution to the dorsal nucleus being only the start of this process. Seen in cross section beyond the dorsal nucleus, the tract appears as roughly V-shaped, but with a fin extending medially along the surface of the thalamus, toward the pretectal region. Cells lying along and below the fiber tract appear to be synapse stations for tract fibers, as well as do the more discrete anatomical nuclei usually assigned to the visual system. In general, the larger fibers distribute over the anterior end of this fan, the smaller over the posterior end, although some fibers of all sizes are present at any level.

The significant feature of this distribution appears to be that separate groups of fibers, from the retina on, as distinguished by threshold for electrical stimulation and by conduction rate, supply these various regions. This may be contrasted with the usual interpretation, that in the propagation of sensory impulses toward the brain, one collateral of a given fiber synapses in the thalamus with a neurone carrying the impulse to the cortex, another collateral of the same fiber passing to secondary nuclei of thalamic or reflex

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gion where the dorsal nucleus of the geniculate passes over into the pulvinar, but it is difficult to say whether this is, properly speaking, geniculate territory. This forms no exception to statement made previously that only the first spike process appears to activate the cortex; for while the post-ganglionic responses can be detected locally, no increase is seen in cortical response when they appear. Work tracing such responses further is in progress, together with degenerative experiments after electrolytic lesions in critical areas.

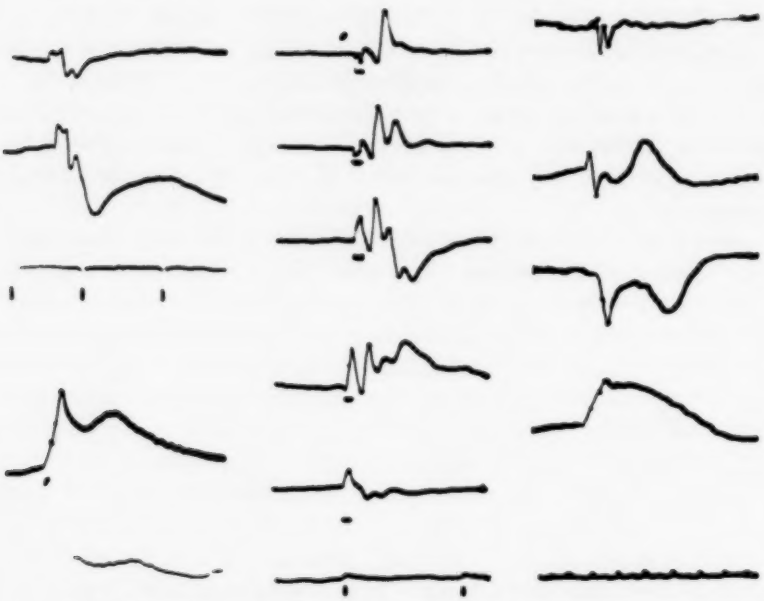

FIG. 6. Records of post-ganglionic responses to optic nerve stimulation elsewhere than from the dorsal nucelus of the geniculate. Left, weak stimulus, first tract and radiation spikes, and below, stronger stimulus, second tract wave and start of a post-ganglionic response. One needle in margin of tract adjacent to medial geniculate, where most of large fibers have left tract to enter lateral geniculate; one needle in hippocampus dorsal and medial. Time 5 msec. Below, record on slower time line of same response to show late response (amplifier connections reversed, record inverted from above). Bottom, same, needle withdrawn 0.5 mm. with marked decrease in amplitude, needle now in groove behind lateral geniculate. Middle column, top, one needle in cut radiation after removal of parietal cortex, one in ventral nucleus of lateral geniculate. Weak stimulus, first tract spike slightly diphasic, and trace of radiation spike. Next, stronger stimulus, ×1.5, second tract spike, half maximal, monophasic. Third record, stimulus ×4, second tract spike becomes diphasic and post-ganglionic response is added. The second spike is followed by a post-synaptic response, and although the spike occupies nearly the same time position as the second spike in the record above, causes a downward deflection, as if the two groups of fibers passed on opposite sides of the electrode. Fourth record, leads one in groove just posterior and medial to ventral nucleus of lateral geniculate, and one deep in brain stem under pretectal region. First tract spike unchanged, second spike no longer diphasic, post-ganglionic spike reversed. The difference between the last two records is due to the fact that the tissue responsible for the post-ganglionic response is between leads in the first case, and outside, or surrounding one lead in the second. This locus corresponds to the ventral nucleus or regions just behind and medial to it. Lower record, leads are the "indifferent" electrodes of two records above, to indicate that the responses do not come from the vicinity of either. The first deflection, as in records above, is stimulus artifact, and a trace of distant responses is picked up as the arm leads will record the electrocardiogram from the distant heart. Time 5 msec. Right column, upper two records, leads from tract to surface of superior colliculus; short DC stimulus, strength for first, maximal for two tract spikes, for second, 6 ×this, just maximal for late response, about 25 ×nerve threshold. Third record, tract to deep colliculus layers, late response reversed; surface negative, deep positive. Note that just preceding the large wave is a smaller one which does not reverse, is recorded as from the tract electrode negative, and appears only at a stimulus strength producing the large post-ganglionic response. Fourth record, slow potential from dorsal nucleus of geniculate in same cat, compare Fig. 1 and Fig. 7. Time 5 msec. The various slopes assumed by the base lines of these and previous figures are due to spontaneous waves of the order of frequency of the cortex alpha rhythm.

function. To be sure, many optic tract fibers do divide, with only one of the branches passing to the lateral geniculate, as Barris, Ingram and Ranson have reported. Our experiments suggest that the characteristic activity of each fiber group is manifest at one locus; that is, that the majority of the fibers which activate the cortex do not activate the superior colliculus, and vice versa.

This situation indicates that in the phylogeny of the visual system, the outgrowth of the geniculate-cortex complex from the thalamic mass may have involved the functional separation of two groups of cells *and their connections* back to the retina, instead of two groups with fiber connections in common, and that the group characterized by the fibers of most rapid con-

FIG. 7. Parasagittal section through lateral and medial geniculate bodies, electrolysis locus of needle giving slow wave of last record, Fig. 6, in cell layers of dorsal nucleus of lateral geniculate.

duction and largest size have come to serve the higher centers. Experiments are now under way to test whether retinal stimulation by light can be so manipulated as to stimulate one group of fibers or another, or whether, perhaps, the same sense organ distributes impulses in the retina to fibers of different groups.

DISCUSSION

Records from any region in the thalamus are written upon the spontaneous slow rhythms present as a base line. In view of the fact that the cortical response to nerve stimulation appears to vary with the phase of the spontaneous rhythm of the cortex, we have recorded thalamic and particularly dorsal geniculate spontaneous rhythms to see whether they were in phasic relationship with the rhythm of the optic cortex. So far this has never been the case, in which we confirm Dubner and Gerard (1939). Moreover, the optic radiation responses to electrical stimulation of the nerve vary neither with

the geniculate rhythm nor with that of the cortex, from which we must conclude that the influence assignable to the alpha rhythm is exerted at the cortical level. We have thus been unable so far to find evidence, in the geniculate, of fibers that would complete a circuit from geniculate to cortex and return, as previously inferred from the circumstance that cutting the radiation either just below the cortex, or even just above the geniculate, abolishes the alpha rhythm. If such fibers exist, they must pass from some structure so near the dorsal nucleus that severing the radiation close to the latter also severs the pathway in question. That is, we should look for a pathway from thalamus to cortex which mixes anatomically with the radiation from the dorsal nucleus, but which converges with it functionally only at cortical synapses; and the origin of this pathway may be expected to be a nucleus reached by corticofugal fibers, and exhibiting a rhythm in phase with that of the cortex. We are the more persuaded that such a pathway will be found to exist since Dusser de Barenne and McCullough (1938) have demonstrated a similar indirect return circuit through an "accessory" thalamic region in the case of the sensorimotor cortex by means of local strychninization.

Allowing for conduction and synapse time in pathways to various parts of the optic mechanism, it appears that of two impulses started in parallel fibers of the optic tract at the retina, the one passing to the cortex will result in a return message to the colliculus, for instance, before the other has reached the colliculus directly. It would thus be possible on physiological grounds for an animal to recognize a sensory stimulus in a shorter time than it could respond to it reflexly; or, looked at otherwise, there would be time for a message from the cortex to reach reflex centers for regulation of the response before the reflex centers were activated directly by the same stimulus. Not only is there time for such a process, but such impulses do arrive at the colliculus from the cortex (Bishop and O'Leary, 1938) and also at the pretectal region. We have not traced them to the ultimate response.

In evaluating the part played by facilitation at the various synapses along the optic pathway, we are inclined to distinguish between the two types observed, the one resulting from a conditioning shock a few milliseconds previous, the other associated with the alpha wave process. The former is similar to that which occurs in the cervical sympathetic ganglion, cord, oculomotor nucleus, etc., and probably will be found at any synapse. The latter may be more characteristic of "spontaneously" active regions. In evaluating the part played by either (or by the interaction of both) in the organization of the response of the cortex to a given sensory stimulus, it will presumably be necessary to go beyond the effect of single or repeated volleys induced by peripheral nerve stimulation, and take into account the pattern of response induced in nerve fibers by activation of sense organs. The problem presents itself in the terms: what is the effect of a given *pattern* of peripheral nerve excitation upon a given *pattern* of cortical receptivity, whether the latter is a function of spontaneous activity or of previous stimulation. In this connection, the statement will bear repetition that the state of cortical

receptivity for extrinsic stimulation seems to be bound up with the activity represented by spontaneous cortical rhythms.

Summary

1. Four groups of fibers in the optic nerve produce four potential waves after conduction. The geniculate and cortex are activated chiefly by the first group of fastest conduction, with one radiation spike only following each nerve volley. Paired shocks exciting these fibers in the optic nerve, even when maximal, show facilitation of the second responses at intervals of 2 to 15 or more msec. The same applies to successive synapses traversed in the cortex, the results being cumulative.

2. The homolateral response of the optic cortex in cats varies from 15 to 70 per cent of the contralateral. No facilitation can be detected at the geniculate level by simultaneous or successive stimulation of the two optic nerves, and little, if any, at the cortical level.

3. Slow potentials of the order of after-potentials in their time relations can sometimes be demonstrated at electrodes thrust into the cell layers of the geniculate. They seem to be non-conducted, and are interpreted tentatively as slow decay of cell body or dendritic excitations.

4. The cortical activity shows a depression followed by facilitation having a phasic relationship to the alpha rhythm, after a single volley in the optic nerve. The short-period facilitation occurring at geniculate and cortex counteracts this depressive phase so that with light anaesthesia responses of the cortex will follow up to at least 100 per sec. Fluctuations of amplitude in these responses still follow the alpha wave set up by the first stimulus of the train, until temporal dispersion of alpha processes occurs.

5. Fibers from the optic tract spread in a thin surface sheet over much of the area bounded by the medial and lateral geniculates, the pretectal area, and the superior colliculus. From regions not usually assigned optic function, post-ganglionic responses can be recorded. In general, the larger fibers with faster conduction rate and lower threshold synapse in the anterior regions of the optic tract distribution, the smaller in the posterior regions.

6. The chief conclusions we can draw from these findings lead to further hypotheses to be tested rather than to an explanation of visual function.

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INTEGRATION OF LOCOMOTOR BEHAVIOR PATTERNS OF THE HAGFISH

BERRY CAMPBELL
Department of Anatomy, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

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INTRODUCTION

THE California Hagfish, *Polistotrema stoutii*, is an ideal subject for the study of simple locomotor behavior patterns. Lacking paired appendages, and relatively unspecialized in nervous makeup, it possesses but one means of progression. This consists of swimming with a sinuous or snakelike undulating action. Progression is normally forward, but proper stimulation will result in a reversal of the pattern and backward swimming. For an account of the mechanics of such progression see Gray (1933).

The undulating behavior, though illustrated well in the hagfish, is not peculiar to it. All fish and aquatic amphibians swim with this method or a derivative of it. Gray (1936) has suggested that this type of locomotion underlies the stepping reflexes of mammals. With this view I am in complete accord. If the stepping reflex is specialization of the undulating pattern, one may say that every species of chordate (except the degenerate adult *Ascidian*) employs the same fundamental plan of locomotion. Thus particular weight must be given to the opinion of de Lange (1936) that the mesoderma segmentation so characteristic of the phylum, as well as the notochord which gives it the name, is no more or less than adaptation for this locomotor behavior.

Considerable error has crept into the older literature concerning the nature of these undulatory waves and the mechanisms by which they move. There is seemingly a natural tendency to link the rate of transmission of the waves with the speed of the nervous impulse over long pathways. For a clear understanding, it must be borne in mind that the actual wave of contraction is a product of local integration and hence the speed is variable. As will be shown below, the waves may stop their motion or go into reverse. Thus they represent not the passage of impulses in descending tracts of the spinal cord touching off the final common pathway, but a wave of excitation of the internuncial as well as the motor neurons.

METHODS

The hagfish were caught in Monterey Bay and kept in large tanks until used.* Ether shaken into seawater served as anesthetic. Operations on the spinal cord were especially easy because no bony or cartilaginous tissue surrounds the central nervous system. The animals are so hardy that extensive operative trauma will not kill them. Spinal shock is minimal. No recording devices were set up; visual impressions of activity were used in interpretation. Because of the possibility of regeneration of nerve fibers all observations were

* I wish to thank the director of the Hopkins Marine Station, Dr. W. K. Fisher, for placing material and equipment at my disposal during the summer quarter of 1939.

made within three days of operation. Stimulation was effected with a Harvard inductorium set to deliver the weakest effective current.

Experimental Results

In the course of the experiments, the brain was pithed in a number of instances. Spinal shock was minimal and characteristics of the spinal hagfish were to be seen as soon as the ether had worn off. Because cephalization is so slight in these animals few deficiencies were evident. The spinal preparations lost the equilibratory reflexes and rolled over when swimming. They became inactive and lay on the floor of the tank for long periods of time. Sufficient stimulation, however, would set them off on long swims during which their locomotion was essentially normal.

When a hagfish is subjected to simple spinal cord section, the anterior and posterior parts of the body acquire a large measure of independence in their behavior. Stroking the tail in the intact animal causes waves of undulation to start immediately behind the head and continue in the normal or backward direction. If, however, spinal section is performed, a new site functions in the initiation, since the waves begin just posterior to the section. This occurs no matter where the cord is divided—even the base of the short tail can serve as site of origin for waves of normal direction. Reverse waves, progressing anteriorly, are the usual result of stroking the gill region. Normally these take origin near or at the tip of the tail. Where the spinal cord is divided, the site of origin of these waves shifts to the part of the cord just anterior to the operation. This occurs when the section is situated anywhere from the tail to just behind the head. The conclusion which must be drawn is that while in intact individuals normal waves generally are initiated near the head end, and reverse undulations near the tail, nearly all segments of the cord possess the ability to initiate waves of both directions.

An experiment was performed which illustrates the nature of the undulating locomotor waves. Hagfish no. 21 was etherized to the point that scarcely any reflexes could be elicited. Then a pair of dull scissors was inserted in the back behind the head and the cord severed by repeated chewing movements. Violent reverse undulations set in which continued for several minutes. As these weakened it was observed that occasionally waves would start near the tail and travel to the anterior part of the body and then slow down. Some would change direction and proceed a short way backwards. These would seesaw back and forth several times. The course of the waves could be governed by stimulation on the surface of the specimen. When they slowed down near the middle of the body a pinch on the tail would start them going posteriorly. Before they reached the tail their direction would change if the gills were stroked. This type of manipulation was possible for several minutes, after which a state of fatigue set in and no activity could be elicited. As in the normal animal, it took a much lighter stimulus on the tail than on the gill region to be effective. It is important to note that the speed and direction of the waves are variable and, though our terminology becomes paradoxical, the waves may be stationary for short periods. What

was observed in this experimental animal was apparently the mechanism which governs much of the activity of the normal one. Stimulation of the gill region causes reverse swimming; stimulation over most of the rest of the body and particularly on the sensitive tail induces forward locomotion. Where both types of stimulation are given, the result depends on the relative strength of the stimuli.

That stimulation of the anterior end of the cord causes the initiation of waves near the tail and vice versa indicates that at the beginning of the activity the cord is functioning as a whole. Striking proof that the undulations continue to be integrated by the entire intact portion of the cord is shown by the fact that the wave-length, from crest to crest, of the bendings are proportional to the length of the integrating segment. In the pithed hagfish this distance may be ten or twelve inches. As the cord is shortened by successive caudal sections, the waves become shorter. Where only the cord posterior to the anus is left, the tail bends into very sharp curves, less than an inch long. Thorner (1932) has observed this phenomenon in snakes. Such findings are adequate proof that locomotor activity is the product of the whole spinal cord and not just those parts innervating the active muscles.

There is much interest in the matter of the coordination between the head and tail ends of an animal with a spinal section. This is the subject of two papers by Ten Cate and Ten Cate-Kasejewa (1933) who, through experiments on the dogfish, confirm the theory of Hooker and Nicholas (1930) that the coordination between front and hind segments of the body is effected by the overlap of proprioceptive sensibility and the consequent reformation of the waves behind the site of section through stretch reflexes. Ingeniously they tested this theory by removing parts of the cord several segments long and by sectioning nerve roots above and below simple sections. From these they concluded that a denervated region of five segments in length is such a barrier to the transmission of undulatory waves that only after locomotion has proceeded in the experimental animal for some time does the rear part show coordination with the fore. Gray and Sand (1936) are unable to support Ten Cate's contention that the rear part of a dogfish can coordinate its activity with the portion anterior to spinal section. They suggest that error may be introduced into Ten Cate's experiments through his reliance on visual impressions of activity. In the experiments which I carried out on the hagfish, visual impressions were also the only method of observation used. Yet the distinct impression was gained that coordination was sometimes possible over complete division of the cord. Several experiments of this type were performed, but in one in particular three sections were made—one immediately behind the head, one at the half way mark, and one behind the anus at the base of the tail. The hagfish survived well and showed symptoms which may help explain the disparity between the conclusions of Ten Cate and of Gray and Sand. Following the operations, it was inactive and lay on its side in the tank. Appropriate stimulation would cause independent swimming movements in any of the four segments, but

locomotion did not result from such activity. When the specimen was persistently handled and subjected to considerable stimulation, the parts would be brought into coordination and it would swim across the tank nearly as well as a normal animal. This successful activity always followed a short period of ineffectual and uncoordinated struggling. My impression was that strong stimulation led to coordinated movements while weak stimulation produced ineffectual and unrelated activity of the parts. This interpretation is supported by the action of animals with spinal hemisections to be described below. It may be that the dogfish which Ten Cate observed had been roughly handled and otherwise subjected to strong stimulation and that those of Gray and Sand, on the other hand, were insufficiently roused. As to the method of coordination between the isolated segments, my experiments shed no light.

In one specimen removal of a section of the cord equal in length to four or five myomeres resulted in a permanent incoordination between the two parts. It must be remembered in comparing this with Ten Cate's more successful operations on the dogfish that because of the absence of a spinal column the hagfish is a much more flexible animal and consequently mechanical transmission would be more difficult.

Hemisection experiments illuminate this matter from another angle. If the spinal cord is cut half way across in a spinal or intact hagfish, striking symptoms are not shown. There is more than usual sluggishness, and the coiled resting posture typical of intact animals is altered. Reverse undulation disappears behind the site of the operation. But forward locomotion is normal. It is not until one makes paired hemisections that striking deficiencies show up. When the two hemisections (on opposite sides of the cord) are situated about 3 cm. apart the symptoms resemble those of a simple complete section in some particulars. In an experiment of this type the protocol showed the following points. Within a few hours of the operation no signs of transmission across the two lesions could be observed. When the head was held, reversing began in the anterior section of the body, the posterior remained passive. When the tail was pinched normal undulations began near the operated segments to proceed toward the tail. Repeated stimulation would sometimes cause the head end to reverse, the tail end to exhibit normal undulation. But the next day there was transmission across the injured region. When waves which started at the head neared the operated segments, they would noticeably slow down with the effect that they became closer to one another. When the head was seized, reverse waves commenced near the paired lesions and only the head end reversed. Continued holding caused the pattern to break through the area of the lesions and the reverse waves began, as in the normal animal, at the tail.

More interesting are paired hemisections when separated by a third or a half of the length of the body. One animal on which this experiment was carried out emerged from the anesthetic, which had been light, in an extremely active state with the highly exaggerated reversings which form the

well-known figure-of-eight writhing of this species. After the animal had quieted down it was noted that, while stroking the snout would cause undulations of the part anterior to the first hemisection, holding the animal by the gills would cause the whole body to reverse in a coordinated manner. The next day it showed a slow, rhythmic, spontaneous undulation of the anterior segment of the body. Waves of rather small but equal intensity passed alternately down each side. But those on the side of the first hemisection, the right side, were stopped at that point, while the left-sided waves proceeded to the second hemisection, where they too were halted. In the middle part of the body, thus, left-sided waves were not accompanied by the usual right-sided ones. The contractions were opposed only by the elasticity of the notochord and associated structures so that between the curvings to the left, the body straightened out, but did not curve to the right. Still, in this animal, a strong pinch on the tail caused rapid and normal locomotion with all segments of the body working.

The unexpected results of the two experiments just described have led me to view the effects of hemisection of the cord as that of a resistance to transmission of locomotor waves. In the first example, the waves slowed down as they approached the lesions. And the reversing, which was confined to the anterior part of the body if the stimulation was light, would break through and involve the whole animal with harsh handling. The latter experiment showed the dissociating effects of the hemisections—right-sided waves could be filtered out, as it were, allowing their counterparts on the left to proceed further down the animal. Yet again, strong stimulation tended to break through and result in normal behavior.

It would obviously be unjustified, on the basis of these gross experiments, to attempt to erect an elaborate explanatory hypothesis, and the comparison, made above, of hemisections to points of resistance must be considered descriptive and not any attempt at theory.

So remarkable did the dissociation of the right and left halves of the behavior pattern by double hemisection seem that direct stimulation of the spinal cord by means of a faradic current was tried. The results check the first observations. When the spinal cord of a hagfish was exposed it was found that placing the electrodes on the right side of the cord caused waves to pass forwards and backwards from the point of stimulation on the right side only. When the electrodes were moved to the left side, the waves affected that side only. Yet it should not be assumed that this effect was due to the stimulation of long tracts, because the progress of the waves was too slow to be due to simple transmission over single or multiple neuron pathways. There is no reason to think that these one-sided waves were not integrated as are the normal ones and thus capable, under proper conditions, of changing both their speed and direction.

The dissociation of the right and left elements of the locomotor behavior pattern focuses attention on the nature of the waves themselves. That such a finding does not mean that the two sides are unrelated in their activity is

indicated by the fact that no manipulation caused waves on one side to pass by those on the other. The left-sided waves were always oriented with respect to those on the right in such a way that they were alternate in placement and travelling in the same direction. The possibility yet remains that an integral part of each wave of contraction is a contralateral wave of inhibition or relaxation.

SUMMARY

1. The California Hagfish, *Polistotrema stouti*, was subjected to operational procedures designed to illustrate the nature of the locomotor behavior patterns. Visual impressions of the deficiencies produced were used for interpreting the results.

2. Simple cord section produces a disintegration of the total behavior pattern which can be reestablished under strong external stimulation.

3. That the behavior studied is a total pattern is indicated by the fact that isolation of a segment of the cord causes an immediate formation of a new site of initiation of the waves and also in that the wave length of the undulations integrated by isolated segments varies with the length of the segments.

4. The undulatory waves represent moving sites of nervous integration and their speed and direction may be experimentally altered.

5. Stimulation of the posterior end of the body and particularly of the tail results in the usual head-to-tail undulations. Stimulation of the gill region initiates waves of reverse direction.

6. Single hemisections of the cord do not incapacitate the animal for forward locomotion, though backward swimming becomes impossible. Paired contralateral hemisections act as complete sections except that with strong stimulation, the pattern was more easily restored to normal.

7. It is possible, with properly placed hemisections, to dissociate the undulatory pattern into right and left-sided halves. Direct faradic stimulation of the sides of the cord also produced this fractionation.

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EFFECTS OF HEATING HYPOTHALAMUS OF DOGS BY DIATHERMY*

ALLAN HEMINGWAY, THEODORE RASMUSSEN, HOWARD WIKOFF AND A. T. RASMUSSEN

Departments of Physiology and Anatomy, University of Minnesota Medical School, Minneapolis, and the Department of Neurology, The Mayo Foundation, Rochester, Minnesota

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THE hypothalamus functions in physiological temperature regulation in two ways. It acts as an integrating and coordinating center for nerve impulses from thermal peripheral receptors (peripheral or reflex temperature regulation) and functions as a "thermostat" since it can activate the heat loss or heat conservation mechanisms when stimulated by temperature changes of the blood (central temperature regulation). This dual function of the central nervous system first described by Richet (1884) has been the subject of a number of investigations of recent years (Fulton, 1938). The exact hypothalamic areas which must be intact for temperature control have been mapped by means of the Horsley-Clark lesion method by Teague and Ranson (1936), Ranson, Fisher and Ingram (1937), and Clark, Magoun and Ranson (1939). The regions of the hypothalamus which are responsive to warmth stimuli have been mapped by Magoun, Harrison, Brobeck, and Ranson (1938) using bipolar Horsley-Clark needles between which a high-frequency diathermy current was passed causing heat without electrical stimulation.

HISTORY AND METHODS

In order to determine to what extent physiological temperature regulation is central or peripheral it is necessary to produce central temperature changes without peripheral changes and vice versa. This is not possible with the usual methods of heating or cooling in which an animal is exposed to a warm or cool environment. With such a procedure *both* peripheral and central temperatures are raised or lowered simultaneously. To investigate central temperature regulation uninfluenced by disturbing peripheral changes, it is necessary to raise or lower the hypothalamic temperature without changing peripheral temperatures. This experiment requires local heating of the brain with a constant skin temperature. Attempts have been made in the past to produce local heating of the brain by cooling or warming the blood passing to, and in some cases from, the brain (Kahn, 1904; Moorhouse, 1911; Barbour and Jelsma, 1931). Barbour (1912) introduced the "warmestich" method in which a heated or cooled metallic cannula was inserted into various parts of the brain thereby producing local heating. These experiments, necessarily acute, have been complicated by anesthesia, surgical procedures, the difficulty in separating blood of the face from that of the brain, and the heating of peripheral structures by venous blood from the brain. Cloetta and Waser (1913) used large external diathermy electrodes outside the skin of the head but this type of heating would heat the skin of the head as well as the brain. The method of Magoun, Harrison, Brobeck, and Ranson (1938) is an improvement over the earlier procedures since excellent localization of heat is produced but anesthesia and surgical trauma caused by insertion of needles through thalamic and hypothalamic structures are possible complicating factors.

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To produce local hypothalamic heating of a normal unanesthetized animal without surgical trauma of the brain small gold diathermy electrodes were placed on the anterior or posterior hypothalami of dogs. Small wires attached to the gold electrode were brought to the skin surface and at least one month allowed for recovery. Quantitative tests for temperature regulatory function such as vasoconstriction, vasodilation, shivering, and panting were made and the responses found to be normal. The brain was then heated by local diathermy and the temperature regulatory responses measured. An anatomical examination of the hypothalamus after completion of the investigations showed the brain to be normal in every respect.

Operative procedure. Nine dogs were carefully chosen for their ability to cooperate in temperature regulation tests not requiring anesthesia. The operation consisted of removal of a bone flap from the temporal region and placement of small gold electrodes with attached wires on either the anterior or posterior hypothalamic areas. The anterior electrode was placed between the optic tracts and extended over the chiasma and to the pituitary stalk. The posterior electrode was placed between the pituitary stalk and the mammillary bodies. The electrodes were approximately oval in shape with diameters of 3 and 6 mm. Two wires, one manganin and the other copper, were insulated from one another and attached to the electrode. The two wires were wound with silk, covered with several thin layers of bakelite enamel and baked in an oven at 100°C. to harden the enamel. Such insulation remains unchanged in all experiments and exhibited no deterioration even after 6–8 months in situ. The electrode wires were fastened to the bony edge of the trephined opening, the free ends of the wires were brought to a subcutaneous position near the mid-line of the superior surface of the skull and the skin flaps sewed over them. Not less than one month after the operation and when temperature responses were normal, as shown by tests, the free ends of the wires were located by x-ray and brought to the exterior through small openings in the skin. In two experiments small gold electrodes were placed in the temporal lobe and in one case a small free thermocouple was placed along the side of the optic tract about 2 mm. from the edge of the electrode. There were no deaths resulting directly from the operative procedure or immediate infection. In one instance a "pus pocket" developed and followed the electrode wires to the brain and extended as a circumscribed area over the pons resulting in the death of the animal 6 months after the operation. There were no signs of infection in the other animals. In the 2 animals described in detail later there was no evidence of damage to the hypothalamus.

Experimental

Tests for normality of temperature regulation. Following the operation the dogs were allowed one month for recovery after which tests were made to determine whether or not the temperature regulatory functions were normal. The physiological mechanisms tested were (i) shivering, (ii) peripheral vasoconstriction, and (iii) peripheral vasodilation and panting. The vasomotor and shivering tests with values for normal responses are described in a previous paper (Hemingway, 1940). Briefly, they consisted of allowing the trained dogs to rest on a shivering recorder in a cool but not uncomfortable room with controlled air velocity, temperature, and humidity. Thermocouples were attached to the skin of the ears, thorax, foreleg, and beneath surface diathermy electrodes of which one was placed beneath the recumbent dog and the other on the upper surface of the thigh. Body temperature was measured by a rectal thermocouple. Temperatures were measured every three minutes during the experimental period. After peripheral vasoconstriction (measured by ear temperature) and shivering had occurred and a steady state of temperatures had been reached, the dogs were heated by diathermy with a heat dosage rate equal to the basal metabolic rate. The heating was continued until peripheral vasodilation, as denoted by a sudden rise in ear

temperature, had occurred. Temperatures were plotted against time on a graph and the threshold peripheral and body temperatures were determined at which shivering and peripheral vasoconstriction commenced and ceased. Similar tests were made for panting in a warmer controlled environment and using diathermy as a means of a measured heat stimulus. The temperature regulatory responses were normal when the threshold temperatures fell within the normal ranges.

Estimation of local brain temperatures. An exact determination of local brain temperature is not possible by the method used for heating. This is due to the fact that the major portion of the heat production occurs in the tissue in immediate contact with the electrode and a steep temperature gradient occurs as the distance from the electrode increases. A free thermocouple 2 mm. distant from the brain electrode indicated body temperature under all conditions of heating. Also the brain electrode was enclosed in a connective tissue sheath which had grown around the electrode in the postoperative convalescent period. Nevertheless, the electrode temperature could be measured with an accuracy of 0.2°C. by means of the attached thermocouple and the heating conditions could be reproduced at any time by adjusting the diathermy current. For each experiment a graph was made of electrode temperature for various heating currents. After this calibration any desired temperature could be obtained by adjusting the heating current.

Electrode temperatures for the various heating currents were as follows:

mA	Degrees C. above rectal
50	0.5°
70	1.0°
100	2.5°
150	4.0°
200	8.0°

The actual brain temperatures were much lower than these upper limiting temperatures due to a connective tissue sheath around the electrode and a steep temperature gradient from the electrode. In the case of anterior hypothalamic heating the optic chiasma was interposed between electrode and thermosensitive hypothalamic tissue.

Local heating of brain. When the temperature regulatory tests had shown that the animals had normal responses to heat and cold the local brain heating experiments were started. In these experiments the dogs were placed on a shivering recorder in an air-conditioned room of 22.0 ± 0.5°C., relative humidity 50 ± 5 per cent and air velocity 25–40 ft. per min. After resting 30 to 90 min., peripheral vasoconstriction first occurred as indicated by a rapid drop of ear temperature and was soon followed by shivering. The mechanical shivering recorder has been described in a previous paper and five degrees of shivering intensity are recognized in an arbitrary classifica-

tion. A shivering intensity 5 represents maximum intensity, 0 represents no shivering, and intermediate degrees of intensity are represented by No. 1–4. The dog lay on his side on a metallic electrode which made electrical contact with his shaved lower side. This lower electrode is the indifferent diathermy electrode, and the skin in contact with this large electrode never undergoes a temperature change when the brain is heated. Skin and rectal temperatures were obtained throughout with thermocouples. When shivering had become sufficiently intense to maintain a steady state of body temperature the brain was heated by passing a high frequency (diathermy) current between the small (active) brain electrode and the indifferent electrode. The currents varied from 40 to 200 mA and were continued for 2 to 20 min. with heating rates of 1 to 5 w. Respiration rate was measured by a chest cuff and tambour. In studying panting similar tests were made except that the room temperature in some experiments was raised to 26°C.

Results

Anatomical. Of the 9 operated dogs two will be described in some detail. These two were the most successful of the series, being free from accidents

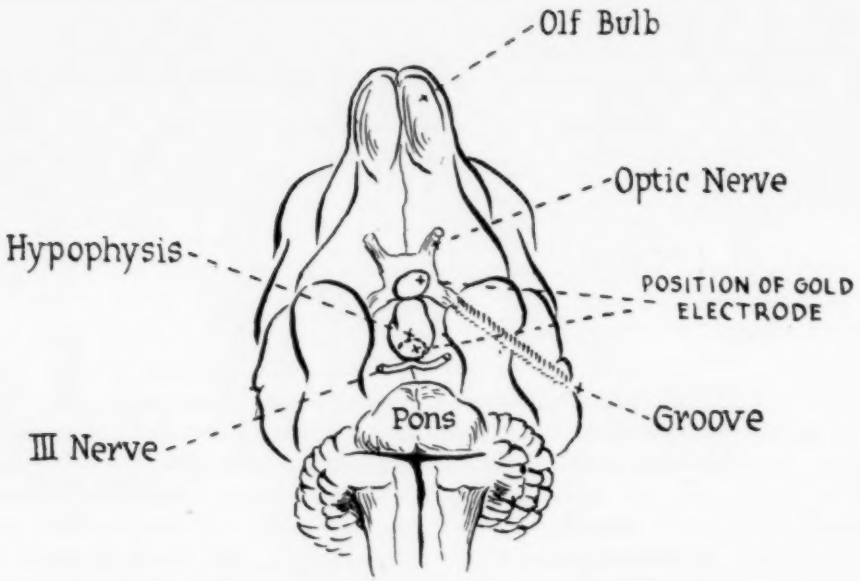
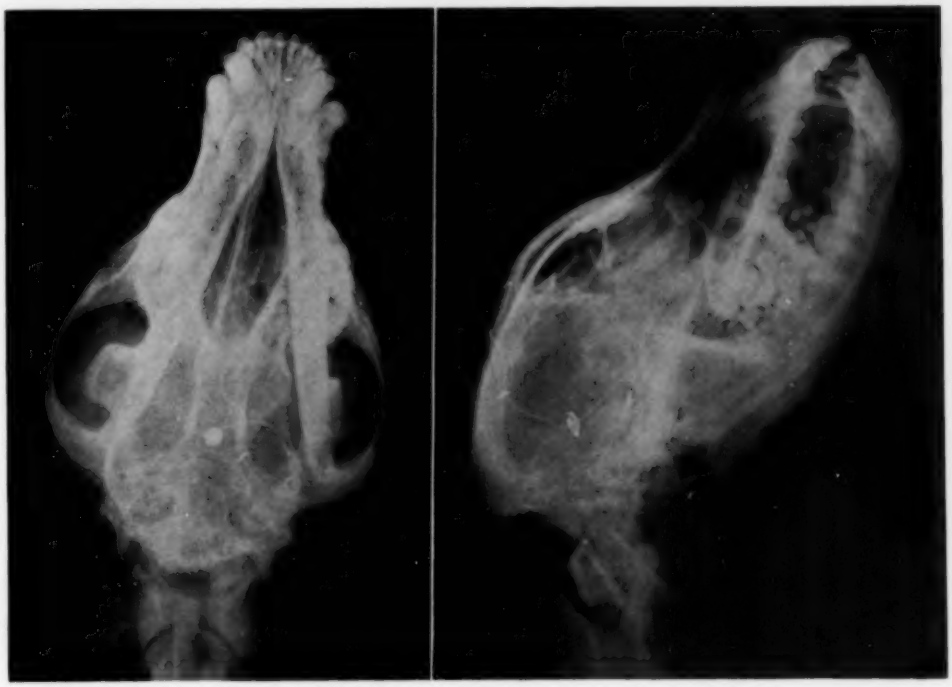


Fig. 1. The position of the hypothalamic surface electrodes is shown. Only one hypothalamic electrode was used on each dog.

and possible errors. The results obtained from the other 7 were confirmatory of the results from the two described. Of these two one had an electrode on the anterior hypothalamus over the optic chiasma and extending to the tuber cinereum (see Fig. 1). The other animal had an electrode on the posterior hypothalamus extending from the mammillary bodies to the pitui-

tary stalk (see Fig. 2B and C). The exact location of the posterior electrodes on the brain is shown in the x-rays of Fig. 2, one electrode being used on each dog. An attempt was made to place both an anterior and a posterior



A B

FIG. 2. A. The position of the posterior electrode is shown by an x-ray exposed from above the head. B. A side view of the same animal.

electrode on the same brain but the dog lived only one week and, since the purpose of the experiments was to have the animals as normal as possible it was considered advisable to reduce hypothalamic manipulation to a minimum and use only one hypothalamic electrode per animal.

A careful histological examination of the hypothalamus beneath the electrodes was made and this region was found to be normal. There was a slight amount of temporal lobe erosion where the electrode wire was in a subdural position but otherwise the brain was uninjured.

Tests for normality of temperature regulation. These tests were made in the manner described, and the temperature regulatory functions of shivering, peripheral vasoconstriction and vasodilation as well as panting were normal. The threshold temperatures fell within the normal range, vasoconstriction and vasodilation rates were normal, and the type of shivering exhibited was that of a normal animal. The panting mechanism was also normal as judged by the respiratory rate-time graphs and the temperature-time graphs. The

numerical and graphical results of these tests are similar to those of normal dogs reported in the previous paper (Hemingway, 1940) and need not be reproduced here. In general, the tests showed normal temperature regulation.

Effects of locally heating the brain. Figure 3 shows the result of locally heating the anterior hypothalamus of a dog resting in a cool but not uncomfortable environment. Before heating, the ear vessels were constricted

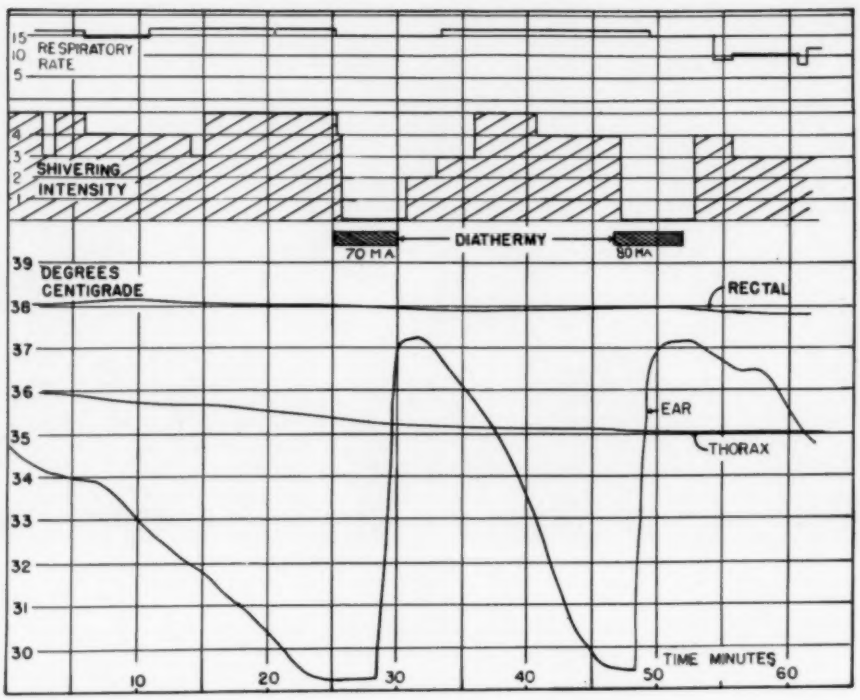


FIG. 3. Effect of locally heating the anterior hypothalamus: Anterior hypothalamic heating causes a sudden cessation of shivering and a rapid peripheral vasodilation. There is no evidence of panting.

as denoted by the low ear temperature of 29–31°C. The animal was shivering rather vigorously. When the diathermy heating current was turned on shivering ceased within one minute and the ear vessels dilated as indicated by the sudden rise of ear temperature. This effect occurred with a heating current of 70 mA and a high frequency voltage of 11.5 v, the heat production rate being 0.8 W. There was no change of trunk peripheral temperature nor rectal temperature. Increasing the current to a value as high as 200 mA did not produce any change in respiratory rate. When the posterior hypothalamus was heated in a similar experiment on another dog (Fig. 4) there was a slight reduction of shivering and no vasodilation with heating rates increased 3- to 4-fold. Drowsiness resulted with posterior hypothalamic

heating and shivering became reduced only when the animal fell asleep. In some cases sleep continued for 5 to 10 min. after the diathermy current had been discontinued and during this period there was reduced or no shivering. As soon as the animal awoke vigorous shivering continued. This was in sharp contrast to the shivering response when the anterior hypothalamus was heated, in which case shivering stopped and started within 1 min. of onset and cessation of the diathermy current.

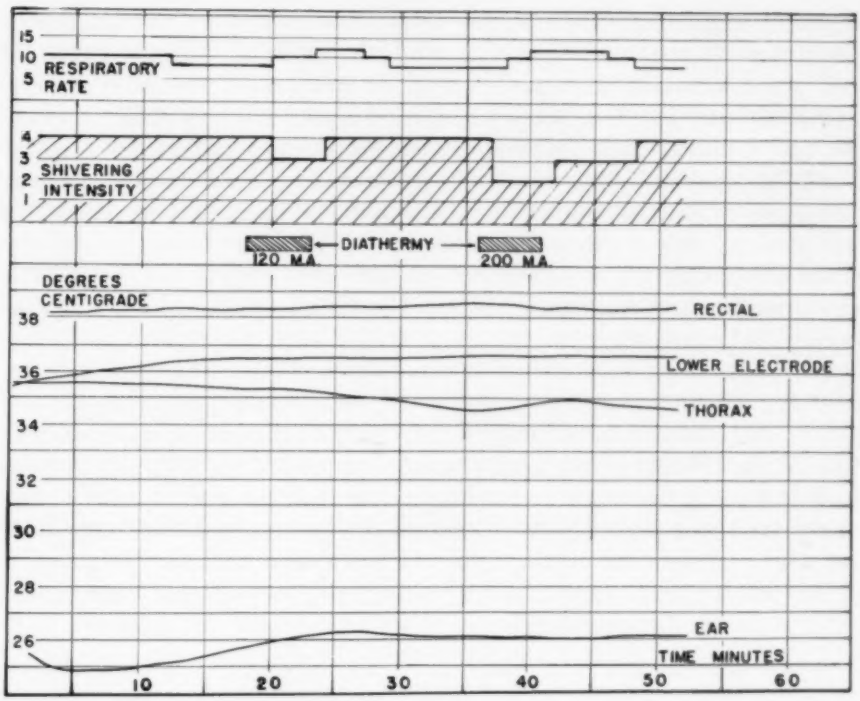


FIG. 4. Effect of locally heating the posterior hypothalamus. A relatively high current value causes a slight reduction in shivering but no peripheral vasodilation. There is no evidence of panting.

DISCUSSION

Quite different physiological effects are produced when the anterior and posterior hypothalamic regions are heated without changing peripheral and rectal temperatures. Shivering is almost instantaneously suppressed and peripheral vasodilation rapidly follows localized anterior hypothalamic heating. When the posterior hypothalamus is heated under similar conditions there is only a slight reduction of shivering and no peripheral vasodilation. This finding furnishes additional evidence to the theory that the "center" for heat loss is located in the anterior hypothalamus above the optic chiasm. It also proves that this region can stimulate the heat loss mechanisms in response to temperature changes of the cells of that region. In this respect

it behaves like the respiratory center of the medulla oblongata which is stimulated by changes in the carbonic acid content of the blood but differs in the fact that the hypothalamic stimulus is physical rather than chemical. The anterior hypothalamus may also serve as a coordinating and integrating center for nerve impulses from peripheral thermal receptors but further investigations are needed to separate more distinctly the anatomical and physiological mechanisms of reflex and central control before conclusions can be drawn.

Uprus, Gaylor and Carmichael (1935) made observations on the body temperatures of patients at which shivering started and stopped. They reached the conclusion that cessation of shivering was an inhibition evoked by a central stimulus. Our results obtained by an entirely different type of experiment are in accordance with their conclusions.

That the anterior hypothalamus is much more responsive to local heating than the posterior hypothalamus when heat loss mechanisms are involved is indicated by the following considerations. The anterior hypothalamic electrode of the dog whose experimental data are given in Fig. 3 was located mainly beneath the optic chiasm. When the tissue beneath the electrode was heated by diathermy the chiasma tissue would have the highest temperature while the hypothalamic tissue above and further from the electrode would be only slightly warmed. In spite of this intervening tissue a diathermy current of only 70 mA produced the striking changes of Fig. 3. When the posterior hypothalamus was heated a current of 120 to 200 mA, and hence producing 4 to 5 times as much heat, caused only a slight reduction in shivering, and this electrode was in immediate contact with hypothalamic tissue. One can conclude from these observations that the hypothalamic heat loss "center" is located just above the optic chiasm and is at some distance from the surface of the posterior hypothalamus.

	To arrest shivering	To cause peripheral vasodilation
Surface heating	2.26 Kcal.	9.0 Kcal.
Hypothalamic heating	0.013 Kcal.	0.032 Kcal.
Ratio	174	281

An advantage of diathermy heating is that the heating rate can be accurately controlled and measured. In the tests for normality of temperature regulatory function the dogs were heated by large diathermy electrodes applied to the skin with a heat dosage equal to the basal metabolic rate. In order to show the sensitivity of central heating in comparison with surface heating the heat production in Calories required to induce shivering and vasodilation by (i) hypothalamic heating and (ii) surface heating with large electrodes has been computed for the dog of Fig. 3. If one considers the anterior hypothalamus as a physiological thermostat, then hypothalamic

heating is equivalent to applying heat directly to the thermostat control whereas heating the entire animal raises the thermostat temperature only when the entire system is raised in temperature. These values prove beyond all doubt the existence of a thermal sensory region in the anterior hypothalamus.

One rather astonishing fact was the absence of panting. The experiment had been originally planned to measure this expected result of hypothalamic heating and all the more so after the appearance of the work of Magoun, Harrison, Brobeck and Ranson (1938) who produced panting in anesthetized cats by diathermy heating of the anterior hypothalamus using bipolar Horsley-Clark needles as electrodes. Our results indicate that either panting requires a more powerful heat stimulus than was given (with currents exceeding 200 mA the dog shows signs of discomfort) or that the sensory center for panting is located further from the hypothalamic surface than the shivering inhibitor and thermal vasodilator centers. This latter suggestion is supported by the brain transection experiments of Lilienthal and Otenasek (1937), *i.e.*, that in cats a region high in the thalamus had to be intact and in connection with lower parts of the central nervous system for panting to occur.

At the beginning of the experimentation it had been intended to complete the work by anesthetizing the dogs and heat coagulating the brain tissue beneath the electrodes by a massive diathermy current. The heat coagulated area would then have given an exact anatomical outline of the heated tissue. This procedure was abandoned for the following reason. If the brain tissue had been heat coagulated a post mortem examination would not have revealed whether or not the brain had been normal when the mild heating experiments had been performed. Anatomical inspection of the brains revealed that the hypothalami of the animals used were normal in all respects.

Summary

Small gold foil electrodes, 3 × 6 mm. in size approximately with insulated thermocouple wires attached, were placed on either the anterior hypothalamus or the posterior hypothalamus of dogs by a subtemporal approach to the base of the brain. The free ends of the electrode wires were brought to a subcutaneous position on the skull and the dog allowed not less than one month to recover from the operation. Tests were made to determine if the temperature regulatory functions of shivering, panting, and peripheral vasoconstriction and vasodilation were normal. When these functions were normal the brain was heated locally by diathermy current from the brain electrode in a controlled environment. Heating the anterior hypothalamus caused inhibition of shivering and vasodilation. Heating the posterior hypothalamus produced sleep and a slight decrease of shivering intensity. Panting was not induced by local hypothalamic heating. The results prove the existence of centers for shivering inhibition and thermal vasodilation in the

anterior hypothalamus which are motivated by local brain temperature changes without changes of general body temperature or peripheral temperatures. Postmortem examination of the hypothalamus revealed that no hypothalamic structures had been injured in any way by the experimental procedures.

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RÔLE OF NEOCORTEX IN REGULATING POSTURAL REACTIONS OF THE OPOSSUM (*DIDELPHYS VIRGINIANA*)*

REGINALD B. BROMILEY AND CHANDLER McC. BROOKS
Department of Physiology, Johns Hopkins University School of Medicine, Baltimore

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KNOWLEDGE of the rôle played by the cerebral cortex of various mammals in the control of somatic motor responses has been obtained in many instances by a study of the deficiencies resulting from partial or complete decortication (2, 9, 11, 13). The easily tested placing and hopping responses have been employed to advantage in such comparative studies (1, 2, 3, 4, 6, 18, 19). This work has furnished a good demonstration of progressive corticalization of control since the deficiencies observed in higher forms are much more extensive than are those resulting from comparable cortical lesions in species which are generally considered to represent a lower level of development.

The opossum (*Didelphys virginiana*) represents an order of mammals which possesses characteristics quite different from those of the mammals previously studied in this way. There are also some similarities. Movements of the facial and limb musculature of this marsupial can be produced by electrical excitation of certain areas of the cerebral cortex (7, 8, 12, 15, 16, 20). Opossums likewise possess hopping and placing responses and are capable of many reactions requiring a high degree of muscular coordination. It was felt that a study of the rôle played by the cortex in the control of these specific somatic motor responses would yield some interesting results.

METHODS

A litter of 10 young opossums was obtained just when they had begun to leave the pouch. They consequently must have been at least 90 to 100 days old. Their reactions were tested at this time; electrically excitable areas of the neocortex of one hemisphere were delimited and various portions of the cortex then ablated. Six weeks later, during which interval the animals' reactions were tested weekly, 6 opossums were again anesthetized and the normal hemisphere exposed and stimulated. The entire neocortex of that hemisphere was extirpated in two animals at this time; the other animals were autopsied. Two surviving opossums were kept for one additional month. Cortical remnants were again stimulated after this period and the brains and spinal cords preserved for further study.

Electrically excitable areas of the neocortex of 8 adult opossums were delimited. Hemidecortication or various cortical lesions were made immediately following stimulation. The placing and hopping reactions of these animals were tested periodically. One month later two of them were again operated upon. Six weeks after the first operation those remnants of neocortex which remained in these 8 adult opossums were stimulated and the animals then autopsied.

Electrical exploration of the cortex of one hemisphere was performed in 10 young opossums which must have been 90–100 days of age, 6 animals 150–160 days old and 8 adults. Light ether anesthesia was used in all cases and the stimulator employed delivered a 60-

* A preliminary report of this work was read before the American Physiological Society 1940 (*Amer. J. Physiol.*, 1940, *129:* 319–320).

cycle sinusoidal wave. Voltage and current strength were recorded simultaneously during stimulation. A unipolar electrode was used for exploration of the cortex, the indifferent electrode being placed on the abdomen.

In ablating various small areas of the cortex, the tissue was first isolated from surrounding cortex with a sharp knife and then removed by means of a narrow-tipped pipette and gentle suction. In 4 adult animals we attempted to study degenerative changes in the pyramid by means of Marchi techniques. These preparations were not very satisfacrory, possibly because the tissues were not obtained until 3 to 6 weeks after operation. The animals were not sacrificed sooner since we were chiefly interested in ascertaining the permanent state of their deficiencies.

Results

Electrical stimulation. The results obtained from stimulation of the neocortex were for the most part similar to those reported by Herrick and Tight (8), Gray and Turner (7), Weed and Langworthy (16) and Vogt and Vogt (15). Even with relatively weak stimuli (1.5 v and 0.2 mA), however, definite isolated movements of the contralateral hindleg were elicited in 6 of the 10 young animals and in 2 of the 8 adults stimulated. Combined fore- and hindleg flexion was obtained in 12 of the 18 preparations. These hindleg movements were elicited from similar areas on the hemispheres of the several animals. A foreleg area lying just rostral to the region from which hindleg movements were obtained was more extensive and by far the most easily defined excitable area of the cortex. Extension of various toes, movements of the wrist, flexion and extension of the arm were also elicitable. Tail movements could occasionally be evoked by stimulation of the dorsal surface or the medial aspect of the hemisphere near the hindleg area. In 5 animals a small area on the lateral portion of the hemisphere gave rise to movements of the contralateral ear. Approximately a third of the animals exhibited respiratory acceleration when the cortex just rostral to the orbital fissure was stimulated. In addition to these rather clearly localizable effects other responses occurred such as movements of the nose, vibrissae or lips, rotation of the head, masticatory movements and closure of the contralateral eye. In some instances stimulation of a small area caused movement of the nostrils toward the contralateral side and excitation of a neighboring area provoked a movement toward the side stimulated. Contractions of facial musculature most commonly occurred when the region rostral and lateral to the orbital fissure was stimulated. One of the major difficulties encountered in attempting to determine the precise boundaries of the area from which a specific movement could be obtained was the fact that a given area failed to respond to repetitive stimuli. In many instances the movement could be evoked two or three times but after that the area remained unresponsive for several minutes. Foreleg movements, however, could be elicited at will and usually from a given point identical responses occurred. The results obtained in the adult were much less satisfactory than those given by the young opossums. Stronger stimuli were required, fewer isolated movements occurred and some responses frequently seen in the young animals did not appear in the adult. Figure 1G and H presents a diagrammatic summary of the results obtained in one young and one adult opossum.

Normal reactions. A study of certain normal somatic-motor reactions of these animals and the effects of various cortical ablations demonstrated that the electrically excitable area exerts some control over these responses. The opossum has hopping and placing reactions which are similar to those of other mammals. They are, however, much slower, less easily evoked and less exact than those of higher forms. In certain species special developments apparently accentuate the importance of some of these responses but in other forms postural or locomotor peculiarities render certain placing and hopping reactions less essential. Because of their highly developed anti-gravity mechanism, their posture and method of locomotion, dogs and cats are more dependent on the hopping responses than is the opossum. Like rats and monkeys, opossums tend to rotate their feet and grasp objects with which they come into contact. The arboreal life of this animal requires such placing reactions but their ready elicitation interferes with the elicitation of the hopping responses and modifies certain other placing reactions. The tendency of opossums to become absolutely passive also adds to the difficulties of adequately studying their postural responses.

Opossums show fairly good visual placing and in blindfolded animals the feet tend to place when the vibrissae come in contact with an object. The head and snout, however, are so long and the forelegs so short that the feet cannot be placed before the chin touches if the animal is held by its hind parts and lowered toward an object. If held parallel to a table edge an animal will frequently reach sideward and grasp the table. This occurs in the blindfolded opossum when the vibrissae touch.

If the forelegs of an opossum are held until the chin is brought in contact with the edge of a table both feet are raised and placed beside the jaws or the table edge is grasped. In executing this response the feet are frequently lifted higher than necessary and the reaction is much slower than that of a cat or rat (1, 4) although it is much faster than the alligator's response (3). The legs practically never extend, as in the cat, to lift the fore parts into a standing posture.

When the fore- and hindfeet are brought in contact with an object which the animal cannot see they are lifted and placed on the object. The response is slow and the feet are lifted unnecessarily high. Frequently the feet are rotated and the object is grasped. The latter practically always occurs when the sides of the feet make contact first. If any leg is forced into an awkward position or pushed off the edge of a table on which the animal is standing the leg is slowly but immediately replaced in a normal position.

The fore- and hindlegs show hopping reactions in response to adduction or strong abduction. The animals frequently grasp and cling to any irregularities of the surface on which they are being tested. In addition they occasionally endeavor to keep their legs in a normal relationship with the body by a type of shuffle which can be roughly described as a sideward movement of the foot by pivoting on the heel and then on the toes. The hopping reactions which do occur are more ponderous and much slower than those of

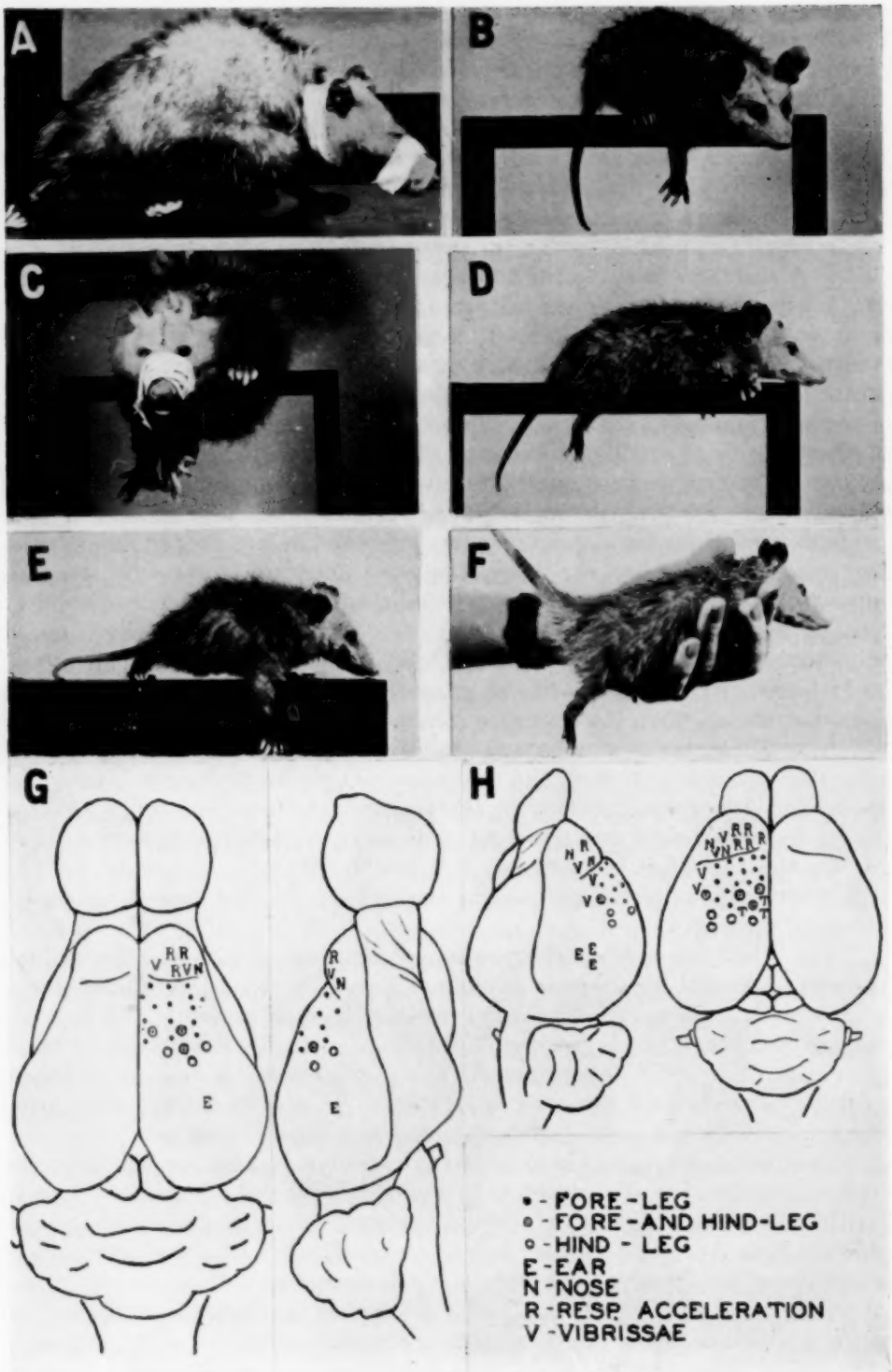

FIG. 1. (See next page for legend.)

higher forms. These reactions as well as the placing responses described above are fully developed in 90–100 day-old opossums.

Effects of cortical ablations. Unilateral ablation of the electrically excitable areas from which leg movements were obtained in 2 young and 4 adult animals resulted in a complete loss of contact placing responses in the limbs contralateral to the lesion. Proprioceptive responses were still present though probably somewhat impaired. Strong retroflexion of a limb caused it to be placed in an approximately normal position. Chin placing was abolished (Fig. 1C) and the legs frequently assumed or could be placed in abnormal attitudes. In walking the animals frequently stepped or stood on the backs of their affected feet (Fig. 1A) and when standing on a bar or near the edge of a box one or the other affected leg commonly was not replaced if it slipped or was pushed out of position (Fig. 1B, D, E, F). Visual placing was likewise impaired and the hopping reactions were decidedly subnormal. Bilateral removal of this area resulted in bilateral deficiencies. Young animals were much more active than were the adults and consequently seemed to be less affected by the lesions. Careful tests revealed no detectable differences in the deficiencies. Young animals did not recover their placing responses and the hopping reactions were permanently defective in both young and old opossums (5).

Complete unilateral ablation of the neocortex in 4 young and 2 adult opossums produced no greater deficiencies in these postural responses of the contralateral limbs than had been observed to result in other animals from unilateral removal of the sensorimotor area alone. Visual impairment was, of course, greater in those animals from which the occipital portions of the neocortex had been extirpated. In one young and one adult animal the entire neocortex of one hemisphere and the electrically excitable area of the other side were ablated. The placing and hopping reactions of the limbs of the two sides were equally deficient.

In one young opossum an endeavor was made to remove the foreleg area alone and in two the area from which hindleg movements had been evoked. All three showed both fore- and hindleg deficiencies. Although they could be distinguished from animals with more extensive lesions we were not al-

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EXPLANATION OF FIG. 1

A. Postural abnormalities in an adult opossum following ablation of the electrically excitable areas of neocortex of the left hemisphere. Animal is standing on dorsum of right forefoot. The right hindleg is abnormally abducted.

B and D. Young opossum which shows defective placing responses in the right legs following a left hemidecortication.

C. Failure of the right legs of the animal shown in A to place when chin is rested on a bar.

E and F. Failure of the foreleg and hindleg to place normally following ablation of the left sensorimotor cortical area. The postures were assumed by the animal.

G. Diagram of the brain of an adult opossum showing the points from which various movements were obtained on electrical stimulation.

H. Similar diagram of the brain of a young animal.

ways able to tell by testing the responses which animal possessed the "foreleg" lesion.

Extensive lesions in the occipital cortex of 3 young and one adult opossum produced visual deficiencies but no impairment of the contact placing or the hopping responses. In one young opossum the neocortex of one hemisphere and the occipital cortex of the other were extirpated. Reactions in the legs opposite the intact electrically excitable area were normal. The cortex rostral to the orbital sulcus of one hemisphere was ablated in another animal. No observable deficiencies resulted.

An abnormality of the grasping responses was noticed in the 3 animals with unilateral ablations of the electrically excitable area. Objects with which the feet came in contact were not grasped as frequently with the affected as with the normal feet. The deficient feet did on occasion grasp objects quite firmly. A finger or a small rod placed in an animal's normal hand was grasped but if one endeavored to lift the animal in this way it let go. If the affected hand gripped the finger or rod the animal could be lifted from the ground and it usually hung on until some extraneous activity caused it to lose its hold. It thus appeared that the affected hand grasps less readily but having done so it cannot let go with normal ease. The hindleg showed this same tendency, but less definitely. This abnormality of grasp response should be studied more thoroughly before being compared in any way with the grasp reflex of monkeys (13).

In the young animals which were kept for several weeks after partial or complete ablation of the sensorimotor cortex of one hemisphere changes were observed to have occurred in the pyramidal tract above the decussation. The ipsilateral pyramids of the 3 animals in which small lesions had been made were reduced in size. Complete hemidecortication or removal of the electrically excitable area caused an almost complete disappearance of the ipsilateral pyramidal tract. Our Marchi preparations like those of Turner (14) did not show degenerating pyramidal fibers below the upper cervical region of the cord but the preparations were rather poor. We have no basis for judging whether a pyramidal or extrapyramidal system or both are responsible for the effects obtained by electrical stimulation of the cortex. We do know that the deficiency-producing ablations do cause degeneration of the grossly visible pyramidal system. This does not indicate, however that the defects observed were due to this alone.

Discussion

The placing and hopping reactions of opossums are slower and less exact than those of higher forms. They are, however, controlled in part by the cortex. As in the monkey, dog, cat, rabbit and rat contact placing is absent following ablation of electrically excitable cortical areas. The opossum's contact placing reaction, consequently, is just as dependent on the cortex as is that of the monkey. On the other hand, cortical removals do produce less change in the hopping reactions than in higher mammals. It, therefore,

seems justifiable to state that the cortical control of these postural reactions is less highly developed in this marsupial.

In the opossum as in the rabbit a hindleg cortical representation is not easily demonstrated but in 11 of the 17 animals stimulated, discrete hindleg movements were obtained. In 8 cases the hindleg flexions were not associated with foreleg movements. The existence of a cortical control of hindleg reactions was likewise demonstrated by the fact that ablation of the electrically excitable cortical areas abolished the hindleg contact placing responses and rendered the hopping reactions definitely subnormal.

Electrical excitation of the cortex produced more responses in the young animals than in the adults studied. There may be certain periods of an animal's development during which the system stimulated is more susceptible to electrical excitation. Possibly due to the smallness of the brain in young animals or the greater permeability of the tissue a larger number of sensitive cells lie within the effective field of the electrode at any given strength of stimulation.

Summary

Electrical stimulation of the neocortex in 17 opossums revealed various areas from which movements of the contralateral facial, foreleg and hindleg musculature could be obtained.

The placing and hopping responses of the opossum are much slower and less exact than those of phylogenetically higher forms.

These postural responses are controlled in part by the electrically excitable areas of the neocortex. Ablation of this sensori-motor area of one hemisphere produces deficiencies in the responses of the contralateral foreleg and hindleg.

The deficiencies in postural adjustment resulting from cortical lesions are less extensive than those resulting from ablation of similar areas of the cortex in higher forms.

Visual responses are affected by removal of the visual cortex but with this exception lesions in non-excitable portions of the cortex cause no deficiency of the postural responses studied.

Extirpation of a portion of the sensori-motor area produces deficiencies which are less extensive than those resulting from ablation of the entire area. Bilateral ablation of electrically excitable cortical areas results in bilateral deficiencies.

Unilateral removal of the electrically excitable area alone produces just as great deficiencies in the placing and hopping responses of the contralateral legs as does ablation of the entire neocortex of one hemisphere.

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CHEMICAL CONSTITUTION AND ANESTHETIC POTENCY IN RELATION TO CORTICAL POTENTIALS

HENRY K. BEECHER

Anesthesia Laboratory, Massachusetts General Hospital, and Department of Physiology, Harvard Medical School, Boston

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IN A PREVIOUS PAPER (Beecher and McDonough, 1939) the cortical electric response to 17 anesthetic agents was reported at two levels of anesthesia, as was the response following sciatic stimulation at each level. While these 17 agents represent many classes of compounds, in a few cases, several members of the same chemical family are present. From observations made on these agents, it appeared desirable to study systematically the relationship of gradually changing chemical composition to cortical effect. The material at hand which was suitable for such comparison was of very limited extent and what there was represented rather extreme changes even within a family of similar compounds. Accordingly, for further study a simple class of anesthetic compounds was chosen, one in which the complexity could be gradually and systematically increased. A homologous series of aliphatic alcohols best filled the requirements.

More than 70 years ago the generalization concerning the relationship of the molecular weight of alcohols to their anesthetic potency which has since come to be known as the "Law of Richardson" was stated. Richardson said " . . . as the weight of the alcohol increases, as the carbon and hydrogen, but especially the carbon, increases, the narcotic action of the agent is increased." This has been supported by numerous subsequent studies. Evidence has also been obtained that the higher forms, the secondary and tertiary forms of the alcohols are more potent than the primary.

It is evident that an opportunity is thus offered for a double check of the possibility of a significant relationship existing between anesthetic potency and cortical response, as well as an opportunity for studying the effect of gradually changing chemical structure of the anesthetic agents on the cortical response. The purpose of the study was to subject these possibilities to experimental test.

METHODS

Animals. Cats were used in all experiments. The right posterior sigmoid gyrus of the cortex was exposed. Activity was recorded from the region of the sensory area in all cases.

Anesthetic agents. Eleven alcohols were employed as anesthetic agents. In the series of normal alcohols the seven agents, methyl, ethyl, propyl, butyl, amyl, hexyl and heptyl were used, and in addition to this series, secondary propyl, tertiary butyl, tertiary amyl, and tertiary hexyl were administered.

Levels of anesthesia. Two levels were used. These were determined by the flexion reflex evoked on electrical stimulation of the central end of the cut left sciatic nerve. The stimulating electrodes consisted of silver wires encased in a rubber tube; the cut sciatic nerve was inserted into this. These electrodes were connected with the secondary coil of a Har-

vard inductorium. In circuit with the primary (activated by a 1.5 v. dry cell) was a hand operated mercury contact key and a string galvanometer signal device. The stimuli were make and break shocks spaced from one to three seconds apart, and usually followed by a rapid series of six or eight shocks (by hand). The ipsilateral nerves to the hamstring muscles were left intact so that a flexor response of the lower leg might occur and be recorded on a smoked drum. The strength of the stimulating current was adjusted to give approximately a maximal response. The two levels of anesthesia were arbitrarily chosen and studied in detail: (i) The lightest anesthesia it was possible to work with without producing a disturbing generalized muscular response, on stimulating the sciatic nerve, and (ii) the level at which the flexion reflex just disappeared. These two levels cover a wide anesthesia range. These two levels will be referred to as light and deep anesthesia. Records of activity at the light level are characterized by greater voltage than those obtained at the deep level and are easier to examine. On the other hand, the light level is somewhat less precise than the deep. Presumably this accounts for the greater variability of the data at the light level than at the deep, as shown in the Table.

Electrodes. The concentric cortical electrodes described by Beecher, McDonough, and Forbes (1938) were used. These are made of silver supported on a hard rubber base. The grid lead is spike-shaped and protrudes 2 mm. beyond the base. It is everywhere insulated except at its tip. At the base it is surrounded by the ground lead, a circular band 1 mm. in width and 6 mm. in outside diameter. The electrodes were freshly chlorided electrolytically each time before use. With these, potential differences were recorded between the surface of the cortex and 2 mm. deep in the interior. When these electrodes are used the ground lead fills a large part of the opening in the skull made necessary in order to identify the desired cortical position. Herniation of the brain is thus in large measure prevented and the arterial and respiratory pulsations minimized.

Amplifier. The potential differences between the grid and ground leads were amplified by the direct coupled apparatus described by Forbes and Grass (1937) and were recorded on film with a Hindle string galvanometer. Ten milliseconds units were recorded by a timer on one margin of the film. The signal device recorded the stimuli on the opposite margin.

Results and Discussion

The standard deviation of the mean* frequency has been calculated in all cases. Frequencies per second of the cortical waves are given. When checked they rarely differed by more than two or three waves per sec. Every deflection was counted as a wave. Care was taken to avoid 60-cycle interference. In each observation activity was usually recorded continuously for 5 to 10 sec. A full second was counted in each case; the seconds, though arbitrarily chosen for counting, were spread out as well as possible over the entire experiment at the given level of anesthesia. The data on frequencies are presented in the Table.

All of the alcohols behaved in regard to their associated electrical cortical activity, as expected, like the volatile anesthetic agents (cf. Beecher and McDonough, 1939). In other words, the pattern was characterized by rapid, fine waves. Sciatic stimulation under light anesthesia produced an increase in voltage of the waves. It also produced a smooth cumulative flexion reflex suggesting that long circuiting of impulses in the nervous system is little curtailed (cf. Beecher, McDonough and Forbes, 1939). No "secondary discharge" (Forbes and Morison, 1939) was definitely elicited in response to

* This is derived by the standard statistical formulae:

$$\text{S.D. (individual)} = \sqrt{\frac{\Sigma D^2}{N-1}} = x; \quad \text{S.D. (mean)} = \frac{x}{\sqrt{N}}$$

To test for significant difference: $M_1 - M_2 > 2\sqrt{\overline{SD}^2_{m_1} + \overline{SD}^2_{m_2}}$

sciatic stimulation. With the heavier alcohols, notably heptyl, suggestive discharges were obtained. These were not definite. Previously, Beecher and McDonough (1939) had reported secondary discharges with amylene hydrate (tertiary amyl alcohol). These were found when the components* of "avertin" were being studied. In the present experiments better grades of alcohols were obtained from the Eastman Kodak Company. In this case, unmistakable secondary discharges were not obtained with any of the alcohols.

Table

Anesthetic Agent Alcohol	Expts.		Counts	Counts	Mean Frequency per sec. With Standard Deviation	
	L	D	Light	Deep	Light Anesth.	Deep Anesth.
Methyl	5	5	80	60	31.5 ±0.3	30.0 ±0.3
Ethyl	6	6	82	77	29.9 ±0.3	30.1 ±0.8
n-Propyl	3	3	58	52	31.1 ±0.4	29.7 ±0.4
n-Butyl	3	3	60	46	29.9 ±0.3	28.5 ±0.5
n-Amyl	3	3	42	44	26.8 ±0.6	25.5 ±0.5
n-Hexyl	3	3	49	43	23.6 ±0.4	21.0 ±0.4
n-Heptyl	3	3	51	54	25.4 ±0.4	21.4 ±0.5
2-Propyl	3	3	45	32	25.8 ±0.5	26.4 ±0.6
3-Butyl	3	3	45	30	27.1 ±0.4	23.1 ±0.4
3-Amyl	6	4	65	58	22.0 ±0.6	21.9 ±0.5
3-Hexyl	3	3	52	41	20.6 ±0.4	19.1 ±0.4

When 4 carbon atoms are exceeded, the alcohol becomes so toxic it is surprising that the relationships elicited held as well as they did. Presumably with the enormous increase in toxicity, side reactions occur which may overshadow the anesthetic action. Studies of this nature usually are terminated with examination of the 5 carbon alcohol, amyl. It has been interesting, however, to continue the study through the 7 carbon alcohol.

While the "Law of Richardson" does not need further support as far as the simple alcohols are concerned, the data contained in Fig. 1 (obtained during the preparation of the animals for the present experiments) have been included for comparison with Fig. 2 where the relationship of specific alcohol to total frequency per second of cortical waves is shown. The rate of change of the curve in Fig. 2 bears an inverse relationship to that of Fig. 1. The total frequency of cortical waves slows with increase in the number of carbon atoms (increase in molecular weight), that is, with increase in anesthetic potency. This suggests a relationship between the total frequency of cortical waves and anesthetic potency, but so far this might only indicate a parallelism between total wave frequency and molecular weight, since molecular weight and potency are related for these compounds. It is possible to go farther than this and to bring out strong evidence that the total cortical wave frequency is related to anesthetic potency rather than molecular weight of the anesthetic agent.

* Tribromethanol in amylene hydrate.

Certain alcohols can be considered as derivatives of methyl alcohol $CH_3 \cdot OH$, called carbinol for this purpose. Normal butyl alcohol $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$, for example, contains the group $-CH_2 \cdot OH$; it may be considered as a mono-substitution product of carbinol, and is called a primary

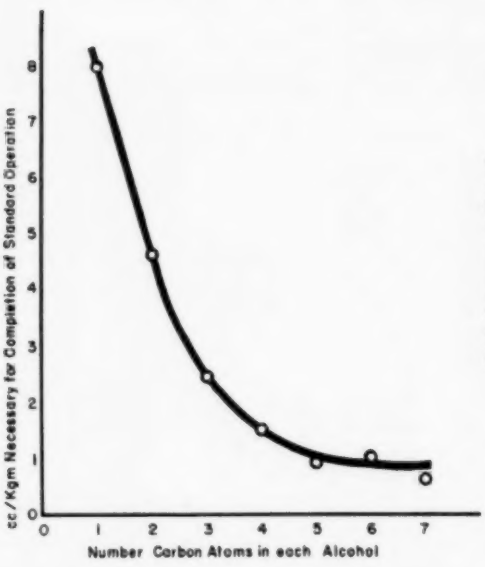

FIG. 1. This demonstrates the increased potency of the alcohols with increase in the number of carbon atoms contained. ("Law of Richardson").

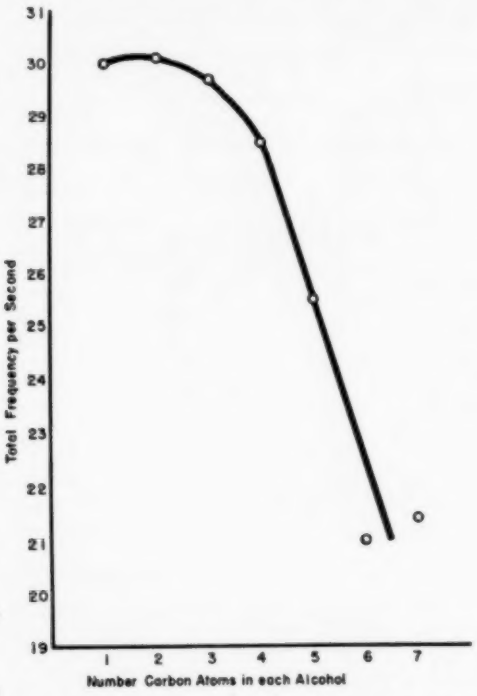

FIG. 2. The relationship of each alcohol anesthesia to total frequency per second of cortical waves. Level of deep anesthesia.

alcohol. Similarly, secondary butyl alcohol $\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CH \cdot OH$ contains the group $>CH \cdot OH$; it may be considered as a di-substitution product of carbinol. Likewise tertiary butyl alcohol $\begin{matrix} CH_3 \\ CH_3 - \\ CH_3 \end{matrix}\!\!>\!C \cdot OH$ contains the group $R_3 C \cdot OH$ and represents a tri-substitution product of carbinol. In these three compounds the variation from one to the others is in structural formula. The molecular weight, the number and kind of atoms remain the same in the primary, the secondary and the tertiary alcohols.

As already pointed out, the secondary and tertiary forms of alcohols are known to have a higher potency than the primary form. This provides another opportunity to observe if the total frequency slows with increased anesthetic potency. Again, a parallelism is shown. (See the Table and Fig. 3.) With the more potent form of the alcohol, the frequency is significantly slower, although in this case the molecular weight and atomic composition

were unchanged. Only the structural form was changed. A significant difference exists in the cases presented in Fig. 3. This has been demonstrated from the standard deviation of the means.*

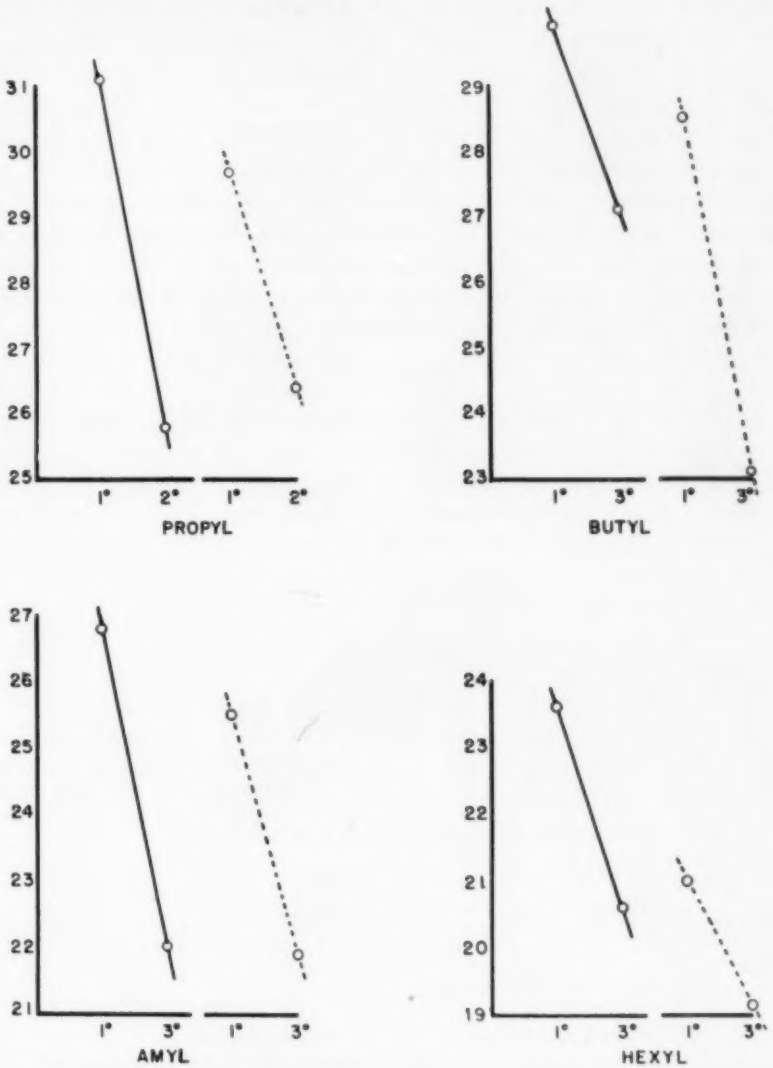

FIG. 3. The form of the alcohol is shown on the abscissa, the total frequency per second of cortical waves on the ordinate. The continuous line represents light anesthesia, the broken line deep anesthesia.

* n-propyl and 2°-propyl: $5.3 > 1.3$
n-butyl and 3°-butyl: $2.8 > 1.0$
n-amyl and 3°-amyl: $4.8 > 1.7$
n-hexyl and 3°-hexyl: $3.0 > 1.1$
As shown here, the difference of the means for the two propyl alcohols, for example, is 5.3, much more than twice the square root of the sum of the standard deviations of the means squared, in this case, 1.3. This is true also for the three other alcohols shown, and the changes are significant.

It would be desirable to have an analysis of the step by step changes produced in the pattern of waves, an analysis which possibly might demonstrate the effects of each additional CH_2 group. It is hoped that such a study can soon be undertaken. The present study is limited, however, to an objective demonstration of the effects of increased potency on one characteristic of central nervous system activity: total frequency of cortical waves. Heretofore, potency has been considered in regard to variations in depth produced by a given quantity or type of agent or it has been considered in regard to variations in quantity or type of agent to produce a given depth of anesthesia. Here, potency has been studied from the point of view of central nervous system activity at a *constant level* of anesthesia produced by a number of different agents. This is a new approach to an old problem which promises to lead eventually to a better understanding of the nature of anesthetic potency and of anesthetic action.

Summary

The cortical electric response to anesthesia from eleven alcohols has been studied in cats in regard to the effects of an increase in carbon atoms in the alcohols and an increase in potency, to the total frequency per second of cortical waves: the frequency becomes progressively slower with increasing molecular weight (increased number of carbon atoms) of the alcohols (Table, and Fig. 2). The rate of change of the frequency curve (Fig. 2) is the reciprocal of that of the potency curve (Fig. 1). That this slowing is due to an increase in anesthetic potency rather than to an increase in molecular weight *per se* is shown by the fact that the total frequency is also slower when the secondary or tertiary forms of the alcohols are compared with the primary (Fig. 3), thus frequency appears to bear a definite relationship to the anesthetic potency of the alcohol, even when molecular weight and atomic composition (but not structure) are maintained unchanged. A new approach to study of the meaning of anesthetic potency is presented.

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OCULAR MOVEMENTS FROM THE OCCIPITAL LOBE IN THE MONKEY*

A. EARL WALKER AND THOMAS A. WEAVER, JR.
Division of Neurology and Neurosurgery of the University of Chicago Clinics, Chicago

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HISTORICAL INTRODUCTION

ALTHOUGH Ferrier (6) and Luciani and Tamburini (12) reported ocular movements upon electrical excitation of the cortex of the angular gyrus and occipital lobe, Schäfer (15) was the first to study these movements in detail. His observations based on the stimulation of the lateral, medial and inferior surfaces of the occipital lobe of the monkey led him to suggest certain connections between the cerebral visual area and the retina—connections which subsequent neuro-anatomical studies have largely confirmed. Later reports have added little to his description. However, all of the investigations were made when little was known of the anatomical limits of the striate cortex or of its connections. The present study aims to correlate physiological and anatomical knowledge of the occipital cortex.

MATERIAL AND METHODS

Twelve adult monkeys (*Macaca mulatta*), convalescent from operations on the spinal cord, were used for this investigation. In none had any operative procedure been carried out on the cerebrum.

Ether or divinyl ether (vinethene) was used as the anesthetic for the operative procedures. A midline incision of the scalp allowed sufficient exposure to remove the calvarium over the occipital, parietal and in some cases the frontal lobes, on one or both sides. The dura was then widely opened and the cortex covered with cotton moistened in warm normal saline.

The cortex was stimulated with bipolar electrodes separated 2 mm. using a sixty cycle alternating sine wave current so arranged that any desired strength of stimulus might be applied.

The ocular movements were observed by one of us seated in front of the animal. Records of the movements were made on bromide paper by passing a suture through the pericorneal conjunctiva after cocainization and attaching it to an upright flexible thin arm which interrupted a beam of light focused upon the camera. Graphic records of the eye movements were not very satisfactory, however, due to the difficulty in registering two-dimensional movements.

RESULTS

Stimulation of the cortex of the occipital lobe and of the adjacent angular gyrus produced slow conjugate deviation of the eyes to the opposite side with or without up or down movements. The response usually had a latency of 1–2 sec. and was 1–2 sec. in completion. The movements were usually smooth, but in the lightly ether-anesthetized animals they were frequently nystagmoid in character. The deviation of the eyes persisted as long as the stimulation was maintained—for periods up to half a minute.

The strength of stimulus necessary to produce these movements varied

* This research was aided by a grant from the Douglas Smith Foundation.

somewhat in different animals but was consistently higher than that required to cause deviation of the eyes by excitation of area 8. Not all points had the same threshold—those about the external calcarine fissure usually

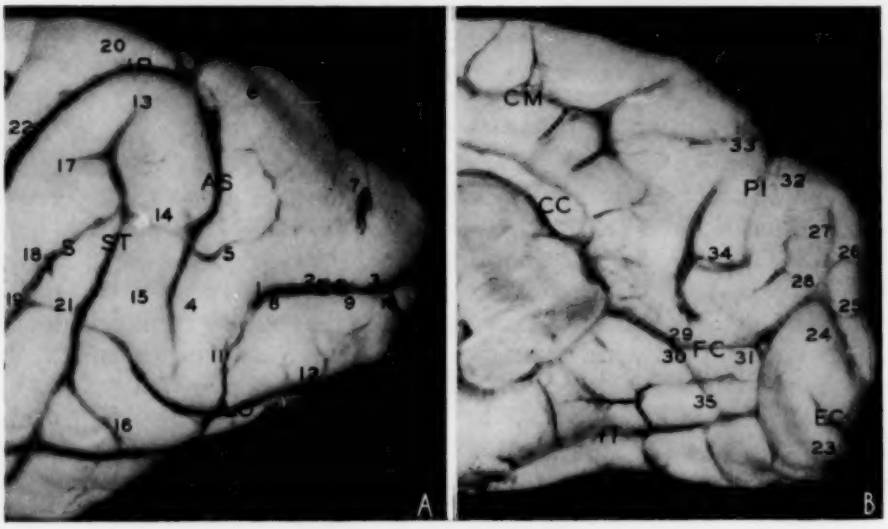

FIG. 1. Photograph of the lateral (A) and medial (B) surfaces of the parieto-occipital lobes of the monkey brain (*Macaca mulatta*). The numbers represent points of application of the stimuli from a composite study of the entire series. The strengths of stimulation varied from 1–5 v. R.M.S. depending upon the site of stimulation, the condition of the animal and the depth of anesthesia. AS, sulcus parieto-occipitalis externus; CC, corpus callosum; CM, sulcus callosomarginalis; FC, fissura calcarina; IP, sulcus intraparietalis; IT, sulcus temporalis inferior; LO, sulcus occipitalis lateralis; PI, sulcus parieto-occipitalis internus; S, fissura sylvii; ST, sulcus temporalis superior; EC, fissura calcarina externa.

1, 2, 3, 5, 6, 7. Conjugate deviation of the eyes to the opposite side and downward.

4. Conjugate deviation of the eyes to the opposite side.

8, to 11. Conjugate deviation of the eyes to the opposite side and upward.

12. Conjugate deviation of the eyes to the opposite side and slightly upward.

13. Conjugate deviation of the eyes to the opposite side with an inconstant downward component.

14. Conjugate deviation of the eyes to the opposite side with an inconstant downward component. Slight pupillary constriction.

15. Conjugate deviation of the eyes to the opposite side with an inconstant downward component. Closure of the eyelids.

16. Widening of the palpebral fissures with slight upward movement of the eyes.

17, 18, 19. Slight conjugate deviation of the eyes to the opposite side.

20, 22. Nil.

21. After a latency of 2–3 seconds slight conjugate deviation to the opposite side.

23, 24. Conjugate deviation of the eyes upward and to the opposite side.

25. Conjugate deviation of the eyes downward and to the opposite side.

26, 29, 30, 32, 33, 34. Conjugate deviation of the eyes to the opposite side.

27, 28. Conjugate deviation of the eyes downward.

31. Conjugate deviation of the eyes to the opposite side and upward.

giving rise to movements with a lower threshold than points near the margin of the striate cortex. The parastriate cortex in general had a still higher threshold. Strengths of stimulation as low as 1.0 v R. M. S. applied to the

striate cortex along the external calcarine fissure produced ocular responses (the threshold for area 8 was under 1 v R. M. S.).

Associated with the lateral conjugate movement of the eyes was frequently a downward or upward component and at times the movement was practically entirely vertical. Although stimulation of the peristriate area occasionally gave rise to upward or downward gaze, stimulation of the medial part of the convexity of the occipital lobe (striate cortex) consistently did so. Excitation of the striate cortex above the external calcarine fissure produced a conjugate deviation of the eyes downward with or without a lateral component. Stimulation below the external calcarine fissure caused conjugate upward movements of the eyes. It was possible to overcome an assumed upward gaze by stimulation just above the external calcarine fissure. By moving the electrodes along the striate cortex, from below to above the level of the external calcarine sulcus (from point 11 to point 5 on Fig. 1) one could cause the animal's eyes to sweep in a semi-circle from an upward to a downward gaze.

On the medial surface of the hemisphere stimulation above the calcarine fissure near the occipital pole produced downward gaze, and excitation below the calcarine fissure upward deviation of the eyes. Stimulation along the anterior part of the calcarine fissure produced conjugate deviation of the eyes to the opposite side with little up or down movement. Lateral movements of the eyes with occasional upward or downward components could be elicited by stimulation of the peristriate area on the medial surface of the hemisphere. After removal of the occipital operculum lateral deviation of the eyes with slight downward components were elicited by stimulation of the cortex of the annectant gyri with a stimulus slightly stronger than that necessary to produce the responses from the operculum.

It must be noted that we have observed on occasions upward deviation of the eyes from stimulation above the external calcarine sulcus. The significance of the observation is not apparent at this time. We have also seen conjugate deviation of the eyes to the ipsilateral side but so inconsistently that we cannot be certain the observation was not a chance movement of the eyes.

Other oculomotor phenomena were not of prime interest in this study. However, pupillary dilatation and constriction, and movements of the eyelids have occasionally been noticed.

Discussion

Ocular movements resulting from stimulation of the occipital cortex have been noted by many investigators in a wide range of experimental animals including dogs (13), cats (12, 13), monkeys (1, 2, 3, 5, 7, 11, 14, 16, 17, 18) and chimpanzee (9). The majority of these papers describe only briefly the responses obtained from the most accessible part of the occipital cortex, namely the operculum. Only Schäfer (15) has explored the occipital lobe in detail and unfortunately he does not give protocols or illustrations

of his experiments. He states that when the electrodes are placed on the upper part of the occipital cortex, either on the lateral or medial surfaces the lateral deviation of the eyes is accompanied by a downward inclination. When they are placed on the posterior extremity of the lobe, its tentorial surface or the inferior part of the medial surface the deviation is accompanied by an upward inclination. From these observations Schäfer (15) suggests that: (i) The whole of the visual area of one hemisphere is connected with the corresponding lateral half of both retinae. (ii) The upper zone of the visual area of one hemisphere is connected with the upper part of the corresponding lateral half of both retinae. (iii) The lower part of the visual area is connected with the lower part of the corresponding lateral half of both retinae. (iv) The intermediate zone of the visual area is connected with the middle part of the corresponding lateral half of both retinae. What an amazingly accurate hypothesis formulated at a time when there was no agreement on the localization of the cortical visual center by all investigators!

That the external calcarine sulcus represents the horizontal meridian is not yet established anatomically today. Poliak (14) is indefinite on this point. Van Heuven (10) and Brouwer (4) place the horizontal meridian well above the external calcarine fissure. From the physiological standpoint the present experimentation favors the suggestion that the external calcarine sulcus is the cortical representation of the horizontal meridian. Unfortunately, few observations have been made on human beings. Foerster (8) failed to obtain eye movements upon stimulation of areas 17, 18, or 19 but elicited a visual hallucination of light in the lower half of the visual field upon stimulation of the superior lip of the calcarine fissure and a similar hallucination in the upper field by stimulation of the inferior lip.

The anatomical pathways for these eye movements have not been investigated in this study. Schäfer (15), however, has shown that the ocular movements produced by excitation of the occipital and temporal lobes are quite independent of the frontal eye fields, for their ablation does not alter the response. Nor does section of the corpus callosum change the reaction. Bernheimer (3) found that the responses were still elicitable after destruction of the superior colliculi and concluded that the pathways probably crossed under the aqueduct of Sylvius. The precise course of the fibers mediating the responses are, however, unknown.

Dusser de Barenne (5, p. 286) believes that the ocular movements obtained by a stimulation of areas 7a and 19a of the Vogts are not cortical in origin since they may be obtained after thermocoagulation of the cortex of these areas. He considers these responses due to excitation of subcortical fibers passing beneath these areas. We have considered this hypothesis as a possible explanation for the movements obtained from the striate cortex. In the acute preparation after thermocoagulation or ablation of the striate cortex, the responses are obtainable from the damaged cortex or white matter with only a slightly higher strength of stimulation than necessary

before the procedure. If, however, the animal is allowed to convalesce for a week or ten days to permit the projection fibers to degenerate and the cortex then restimulated, the specific responses are absent even with strengths of current two or three times the threshold of the adjacent normal striate cortex. It therefore, seems likely that the ocular responses elicited from the striate area are the result of cortical stimulation and not due to excitation of underlying fibers.

Conclusions

Contralateral conjugate deviation of the eyes with lateral, or with either upward or downward components was obtained by stimulation of the occipital cortex. When the exciting electrodes were applied to the cortex of area 17 superior to the calcarine fissure, the movements tended to be lateral and downward. When applied below the same landmarks, the deviation was lateral and upward. The relationship of this finding to the projection of the retina on the cerebral cortex is discussed.

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NATURE OF THE FIRST VISIBLE CONTRACTIONS OF THE FORELIMB MUSCULATURE IN RAT FETUSES

WILLIAM L. STRAUS, JR.* AND GRAHAM WEDDELL
Department of Anatomy, The Johns Hopkins University, and Institute of Anatomy and Embryology, University College, London

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LITTLE is known about the physiological properties of the developing striated musculature of mammals at or near the time of its earliest contractility. Most of the existing observations have been incidental to studies of the ontogeny of behavior, or rather of reflex activity (1, 2, 15, 30). In such instances the characteristics of the visible muscular activity have been regarded, at least by implication, as directly reflecting the intrinsic physiological properties of the muscles involved. No consideration seems to have been given to peripheral structural factors that conceivably might modify the form of the muscular response.

This paper deals with the nature of the first visible forelimb responses to electrical stimulation in rat fetuses. Brief morphological correlations have been made. We have not observed somatic movements in any fetuses up to the 16th day of gestation, even when very strong currents were employed. The earliest visible contractions were secured from the forelimb musculature during the 16th day of gestation. Movements produced by contractions of the neck muscles have been elicited at about the same time, while the trunk and proximal hind-limb muscles become visibly reactive not long thereafter.

Most of the animals studied were white rats, but pied animals were used in a few experiments. According to the data collected by Donaldson (7), no appreciable differences between them would be expected. Twenty-five 15-day-old fetuses, all without perceptible response, were studied. These came from 5 litters (with estimated copulation ages of from 346 to 349 hours) and measured 9.5–12 mm. crown-rump length.

The data presented herein have been obtained from 12 fetuses of 7 different 16-day-old litters (with estimated copulation ages of from 368 to 378 hours), ranging between 12.5 and 14.5 mm. C. R. (nos. 10-2, 11-1, 19-1, 19-2, 20-1, 20-2, 20-3, 25-2, 101-1, 101-2, 101-3, 102-1). Some of these were asymmetrical in responsiveness. Furthermore, not all specimens of this size or age responded visibly to stimulation. Some of the 16-day litters contained both reactive and non-reactive fetuses measuring more than 12.5 mm. We have not observed contractions in fetuses smaller than 12.5 mm. C. R. One other litter of 3 animals (no. 5), estimated to be 371 hours old and measuring 12–12.5 mm. C. R., gave no perceptible response.

Visible, electrically induced contractions of the forelimb musculature of the rat therefore first appear some time during the latter half of the 15th

* Fellow of the John Simon Guggenheim Memorial Foundation, 1937–38.

or the first half of the 16th day of prenatal life. In view of the variability of responsiveness among our fetuses of the latter date, it seems likely that we have been studying specimens at or shortly after the point of transition. Windle *et al.* (30) obtained their earliest responses to electrical stimulation in rat fetuses 368 hours old, 11 mm. C. R. This age agrees with that of our own experience, but their fetuses were about 2 mm. smaller. Possibly this discrepancy is related to a difference in stocks of rats, but more likely is referable to dissimilarity in method of measuring the fetuses.

TECHNIQUE

The experiments were so conducted that the fetuses remained attached to the mother, with circulation intact. Their condition uniformly was good, body-color being used as the chief criterion. This appears to be a good index, because the normal pinkish color of the fetus rapidly changes to a purple whenever the circulation is obstructed or other anoxemic conditions obtain.

The pregnant female rats (except those noted below) were anesthetized by subcutaneous injection of Nembutal (Abbott's Veterinary, no. 8612, each cc. containing 1 grain) in doses of 0.1 cc. per 100 g. of body-weight. The general condition of the mother rat was excellent throughout the experiment, with two exceptions (nos. 16 and 25). Control experiments were carried out in order to ascertain whether the use of Nembutal suppressed or modified the muscular responses. Thus one of the 15-day pregnant animals was studied while under ether, and another after complete section of the thoracic spinal cord, without general anesthesia (over 3 hours being allowed for recovery from ether administered during spinal section). Two of the 16-day pregnant mothers (nos. 101 and 102) were investigated after similar thoracic section, without subsequent anesthesia, by the senior author after his return to the United States. In all of these instances, however, the results obtained were identical with those of the other experiments on fetuses of the same ages. Hence the data secured from the 16-day controls have been included in this communication.

The anesthetized mother rat was tied to a board and her hindlegs and trunk submerged in a bath of physiological salt solution maintained thermostatically at or near a temperature of 37°C. The abdomen then was opened by midline incision and the uterus exposed. The fetus to be studied was removed, with amnion intact, from the uterus to an adjacent submerged shelf composed of several layers of gauze stretched on a wire frame. All experiments were carried out under fluid, the fetus usually lying close to the surface of the bath. Some fetuses were lifted out of the fluid and studied for special points. Most of the observations were made through a binocular dissecting (Greenough) microscope at enlargements up to 10 diameters. Afterwards, the umbilical cord was ligated and severed, the fetus measured under fluid with sliding calipers and finally preserved for histological study.

The fetuses first were observed while in the amnion. The latter then was removed, care being taken to avoid injury to the placental circulation. The fetuses were stimulated electrically through their skin. This was so thin that it offered little obstruction to a current, because when the skin was punctured and the stimulus applied to the muscles directly there was no appreciable difference in the response. Steel bipolar electrodes with fine points slightly less than 0.5 mm. apart were used. These were insulated to the tips to prevent undue loss or spread of current. Faradic current from an inductorium was applied to most of the 15-day litters and to 16-day litters nos. 5, 10, 11, 101 and 102 (these including responsive fetuses 10–2, 11–1, 101–1, 101–2, 101–3, and 102–1). All other fetuses were stimulated with current from a gas discharge valve (thyratron) delivering variable strength condenser shocks ranging in frequency from one shock to 460 per sec. Current strength ranged from 1 to 20 v. Resistances were not determined. Duration of shock (Fig. 1) was approximately 70 μsec. Galvanic current was tried but discarded because of the intense polarization and ensuing damage to the fetus.

Nearly all specimens were subjected to some form of mechanical stimulation, such as with a fine hair or by gentle prodding or displacement of parts; but these procedures did not result in visible muscular contraction except in one specimen, described below.

Physiological Observations on Responsive Sixteen-day Fetuses

(1) *Types of forelimb movements.* In 2 of the 16-day fetuses, 19-1 and 25-2, only shoulder muscles were visibly reactive to electrical stimulation. All other responsive specimens, however, produced more extensive and varied movements, involving shoulder, elbow, and wrist, separately or in several combinations. There was considerable individual variability. Finger movements never were observed. Stimulation of points over the shoulder or in the upper arm often elicited extensive movements, such as abduction of the entire limb accompanied or followed by dorsiflexion (hyperextension) of the wrist. Elbow extension sometimes was included in this movement. Dorsiflexion of the wrist was very easy to produce, this in contrast with movements of the elbow-joint. In 20-3, however, stimulation in the region over the brachial plexus gave rise to a striking diphasic displacement of the elbow, consisting of extension followed by flexion; occasionally this appeared with phases reversed, flexion then preceding extension. In general, the extensor musculature appeared more responsive than the flexor; but this may have been more apparent than real, for the position of the limb at this age is such that the extensors are more easily subjected to thorough experimentation.

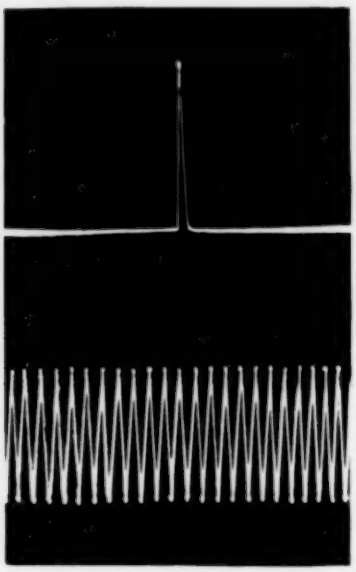


Fig. 1. Form of thyratron shock (above), and a frequency of 10,000 per sec. (below) for comparison.

(2) *Character of movements.* The forelimb movements of 16-day rat fetuses characteristically were of relatively long duration so that, in contrast with the adult, the moving parts travelled quite slowly. Both phases of the movement—active (muscle shortening) and passive (muscle relaxation)—were prolonged, the latter phase appearing to be especially lengthened in most instances. Repeated stimulation tended to lengthen both phases, as with 20-1, in which the movements became perceptibly slower after 8 or 10 responses. There was no indication, however, that the contractions were maintained when a current of liminal duration was applied. The response, therefore, is distinguished by marked prolongation of both phases of the movement rather than by anything suggesting a tonic state of muscular contraction. This typical slow movement was elicited by both methods of stimulation—faradic current and condenser.

Fetus 20-1 was studied to determine the effects of prolonged stimulation. Condenser shocks at a frequency of about 100 per sec. were employed. The

electrodes were kept in contact with a point on the dorsum of the upper arm for at least 10 sec. Not only were both elbow and wrist extended, but they were so maintained in what resembled a tetanic or tonic contraction for the duration of the stimulus. Ensuing responses to stimulation were feeble. That this particular reaction may have been tetanic, is suggested by the response of this same fetus to similar treatment with shocks given at a frequency of 1 per sec. These produced a relatively feeble, clonic tremor.

Fetuses 25-2 and (some movements only) 20-3 were the only specimens in which rapid movements were noted.

The muscles in many fetuses seemed to fatigue rapidly, visible reactions sometimes ceasing after a few responses to stimulation. But their apparently complete recovery following 5 or more minutes of rest in some instances is a proof that this was not the result of injury. Fetus 19-1 gave only one visible response to stimulation, although the experiment was continued for over one-half hour. In all other reactive fetuses, however, the movements were capable of reproduction. Two of the fetuses of rat no. 20 and the three of rat no. 101 differed from the other specimens in that they exhibited no signs of especially early fatigue. These variations appear incapable of explanation at the present time.

(3) *Strength of current.* The threshold of visible contraction in the fetus usually was quite high when contrasted with that of the mother, the maternal m. rectus abdominis usually being employed as a basis for comparison. In experiments where the faradic current was used, movements never were elicited if the secondary coil of the inductorium was withdrawn more than 4 cm. from the primary coil (with a current of 2 V on the latter). This was a much stronger current than that required to elicit contraction of adult rat muscle.

The same occurred, but with some individual variability, when using the condenser shocks. With these, from 7 to 10 V regularly caused contraction of the maternal rectus at a frequency of 100 or less per sec. A much stronger stimulus, ranging from 13 to 20 V, was needed to procure movement in the fetuses. As little as 7–10 V, however, at first produced some visible response in 20-1, but the general threshold soon was greatly elevated.

(4) *Time factor.* In most instances—regardless of the type of current—there was an appreciable interval between the application of the stimulus and the perceptible beginning of a movement. At times this exceeded a second. Indeed, in some instances visible responses could be obtained only after continued or repeated stimulation.

Condenser discharges much below a frequency of 100 per sec. were mostly ineffective in producing movements in the fetuses, although effective in adults. Fetus 20-1 was a notable exception, for, as mentioned above, it showed weak, clonic movements with shocks given at a frequency of one per sec. In addition, with shocks of 100 per sec. this specimen exhibited no appreciable delay of response until a series of rapidly sequential movements was induced. On the other hand, 19-2 failed to respond at a frequency of less

than 150 per sec. High frequency in itself, however, was inadequate if the voltage was too low.

(5) *Excitation through nerves.* In at least 5 of the fetuses it was possible to produce contraction of more distal muscles by electrical stimuli applied to proximal parts of the limb. For example, in some specimens stimulation of certain well-defined points on the dorsum of the upper extremity well above the elbow gave rise to dorsiflexion of the wrist. This was accompanied or preceded by abduction of the shoulder (and in certain instances extension of the elbow), or even could occur as an isolated movement. The possibility of spread seems to be excluded by the fact that stimulation of closely adjacent points caused no response. Return to the original excitable area invariably duplicated the movement. The most reasonable interpretation of this phenomenon is that we are dealing with excitation of muscles through their nerves, and that the excitable areas represent "motor points."

Four fetuses (10-2, 11-1, 19-1, 101-1) were stimulated in the region of the brachial plexus by introducing the electrodes through a skin incision. Three of these experiments produced no visible muscular contraction. In the fourth (10-2), however, typical movements, including the wrist, were obtained. Similarly, electrical stimulation of the skin over the brachial plexus area in 20-3, without insertion of the electrodes, gave rise to contractions of distal forelimb muscles. The movements seemed to vary with the points stimulated. The same results were obtained by pressure applied to this region with a blunt object, but gentle stroking of the skin (touch?) was ineffective. The negative results should not be stressed in view of the technical difficulties involved, but in the positive cases it seems clear that we must be dealing with effective conduction by efferent nerves.

In some instances, indeed, it appeared as if movements were more readily secured via the nerves than by direct stimulation of muscles. For, at times, distant stimulation proved successful when direct stimulation failed.

EXPLANATION OF FIGS. 2-6

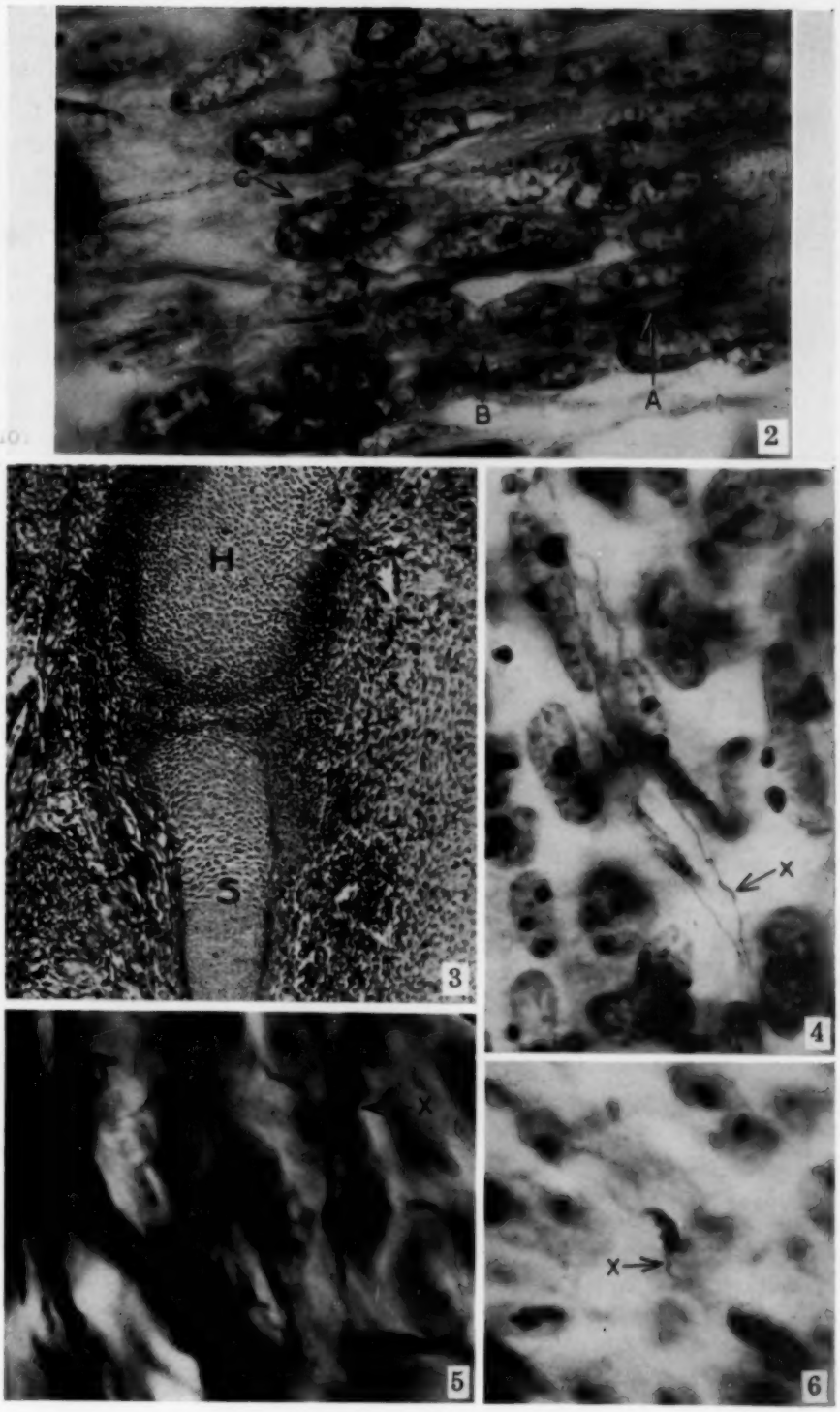
FIG. 2. Section through superficial forearm extensors of 16-day rat fetus (13 mm C. R. length), showing myofibrillae in various stages of development, A, homogeneous fibrillae. B, beaded fibrillae. C, definitive fibrillae. Fixed in formalin-Zenker's fluid, 5μ iron haematoxylin. ×1400.

FIG. 3. Section through shoulder-joint of 16-day rat fetus (13 mm. C. R. length). Space between scapula (S) and humerus (H) occupied by mesenchyme; joint-cavity undeveloped. Fixed in formalin-Zenker's fluid, 5μ, iron haematoxylin. ×90.

FIG. 4. Section through shoulder muscle of 16-day rat fetus (13 mm. C. R. length), showing fine terminal nerve-fibers at X, slightly retouched. Fixed in 10 per cent formalin, 10μ, Bodian's protargol stain. ×1750.

FIG. 5. Section through forearm flexors of 16-day rat fetus (13.5 mm. C. R. length), showing nerve-fiber ending as a bulb at X. Fixed in 20 per cent formalin, 10μ, Cuajunco-Bielschowsky silver stain. ×1750.

FIG. 6. Section through long head of triceps brachii of 16-day rat fetus (13.5 mm. C. R. length). Nerve-fiber coming from above (not visible here) forms a bulb containing neurofibrillar net and continues as a fine, lightly staining, terminal filament (X). Fixed in 20 per cent formalin, 10μ, Cuajunco-Bielschowsky silver stain. ×1750.



FIGS. 2–6. (For legend see opposite page.)

Histological Study of the Forelimb in Sixteen-day Fetuses

The specimens are being studied histologically by one of us (W. L. S.). This investigation has not yet been completed, but it has revealed that the muscle-fibers and other structures within the forelimb of the 16-day rat fetus are morphologically immature.

The walls of the muscle-fibers are extremely thin. The nuclei are prominent and tend to occupy almost the whole width of the fiber. Myofibrils are relatively scarce. They sometimes occur as apparently homogeneous threads or beaded structures. Frequently, however, they exhibit high differentiation, with A and I segments, and in many of these a Hensen's stripe and a Z line also are visible (Fig. 2). Yet in such instances the fibrils are few in number, at times only four or even less to a fiber, so that definitive cross-striation of the fiber as a whole is not yet present.

Muscular fascia is just making its appearance; for, with Mallory's triple stain, little connective tissue is visible. Tendons have not been formed.

The joints are in an early stage of formation. The space between the skeletal elements is occupied by a rather dense mass of mesenchyme, so that articular cavities are not developed (Fig. 3).

Following silver impregnation, numerous primitive nerve-endings can be seen within the forelimb muscles but no motor end-plates such as are present in the adult. These endings are extracellular; they have not been seen within the cytoplasm of the muscle-fiber. Sometimes they appear to lie between the individual muscle-fibers rather than upon them. They assume a limited variety of forms. Most of the fibers terminate as slender threads that seem to fade out beyond the limits of microscopic visibility (Fig. 4). Possibly, however, this merely represents lack of argyrophilia at their ends. In other instances the nerve-fibers end as solid bulbs or loops that sometimes contain neurofibrillar nets; or they possess enlargements that distinctly resemble the growth cones described by other workers, as Speidel 52 (Fig. 5, 6). It is not certain that any of these structures are definitive nerve-endings. They all may represent areas of fiber growth.

Discussion

The visible contractions of forelimb muscles in 16-day-old rat fetuses, induced by electrical stimuli, are characterized by (i) relatively long duration of the movement, involving both its active (muscle shortening) and, especially, passive (muscle lengthening) phases; (ii) comparatively high threshold of excitability; and (iii) relatively long delay of visible response. These properties can be stated only in general terms at this time because of the difficulties of applying more precise physiological procedure to specimens of this age. The deviations in certain features of the response exhibited by some specimens we are unable satisfactorily to explain. Their significance must await further study. These observations confirm and supplement those

secured by Windle *et al.* (30) from direct stimulation of rat fetuses, although these authors noted neither appreciable time factor nor tendency toward early fatigue.

The most obvious interpretation of our results would lead to the assumption that the visible characteristics of the induced movements accurately reflect the intrinsic physiological properties of the muscles involved. If such reasoning be acceptable, our findings indicate that slow contraction, high threshold and long time factor all are common to immature skeletal muscle, as in these 16-day rat fetuses. The long time factor can be interpreted as probably involving both a long latent period and a long muscle chronaxie. The former is suggested by the delay of visible response following stimulation. A long chronaxie would seem to explain our results following stimulation at various frequencies of condenser discharges. The necessity for continued or repeated stimulation, and for relatively high frequency in the case of the condenser—where duration of shock was short—both suggest the phenomenon of summation or latent addition. That this is characteristic of tissues with long chronaxie, is well known (13).

The above conclusion would agree fundamentally with the findings of other workers. Thus the electrically induced contractions of mammalian striated muscle have been found to be slow or of long duration in both young fetuses (4, 30) and older fetuses or new-born or very young animals (10, 15, 20, 22, 24, 28). A marked retardation of relaxation is emphasized by most of these investigators. Contractions likewise are slow in the chick embryo (18) and small amphibian larvae (6, 9, 26, 31). A high threshold of excitability, on both direct and indirect stimulation, often has been noted in fetal and new-born mammalian striated muscle. This is true for both the galvanic (15, 27, 28) and faradic (4, 15, 24, 27, 28, 30) forms of current. Conditions are similar in the chick (18). Some workers have reported a distinct or long latent period for the muscles of fetal or new-born mammals (1, 2, 4, 10, 20) and for chick embryos (17). Furthermore, it has been found that young mammalian skeletal muscle exhibits an exceedingly long chronaxie when compared with adult muscle. The data on this point have been summarized by Quincke and Stein (21). The chronaxie of the 5-day chick embryo also is long, being 60 times that of the adult fowl (16). These results might be expected since there is a direct relationship between length of chronaxie and duration of contraction (14). A tendency toward early fatigue of skeletal muscle by electrical stimulation was noted in our rat fetuses, and has been found in chick embryos (16, 18). Whether this depends upon factors intrinsic to young muscle or upon more general physiological conditions, can not now be decided.

It may be noted that immature skeletal muscle appears to be possessed of certain properties revealed by normal adult striated muscle only in electrically induced reversible contracture: Excessive duration of contraction and long excitation time (long chronaxie) especially as expressed by the

necessity for latent addition or summation (5). In many respects the visible reactions bear a curious resemblance to the Vulpian-Heidenhain phenomenon as summarized by Gasser (8).

Rückert (22, 23) concludes that the "tonic" or contracture-like capacities of a skeletal muscle stand inversely to its ontogenetic and phylogenetic age. In other words, the slow form of contraction is primitive and the rapid twitch advanced. Our observations on rat fetuses appear to support this thesis in so far as individual development is concerned: for the relatively long duration of the movements seemingly point to slow muscular contraction as its basis. It was noted that the muscle-fibers of the 16-day rat embryo differed from those of the adult, being morphologically immature. It would not be surprising, therefore, if the fetal muscle differed physiologically as well.

Not only the muscle, but the entire forelimb of the 16-day rat embryo is extremely immature. To assume that the visible responses accurately portray the physiological properties of the muscles concerned, may accordingly be inadmissable. Muscular fascia is quite rudimentary, while tendons are not yet developed. These are factors that readily may affect the efficient utilization of the muscular contraction. Furthermore, the articulations are in the earliest stages of formation and there are as yet no joint cavities. The limb therefore has the appearance of a relatively rigid structure and the muscles likely are operating upon comparatively stiff levers. In totality, these factors—which may be termed extramuscular—well may influence the nature of the response and produce a visible movement that fails to reflect the true character of the muscular contraction itself. It is entirely conceivable that the limb segments at this early stage may be possessed of considerable inertia relative to the force of contraction produced. It is quite possible that this would influence apparent time factor and duration of movement. Hence the seemingly long latent period, long chronaxie, and slow contraction all may be false phenomena resulting from the modifying effects of the peculiar extramuscular conditions.* Indeed, in view of the necessary experimental conditions, this possibility cannot be excluded. The small size of the fetuses precludes the usual experimental treatment of the muscular tissue, so that comparison with results obtained from adults or even new-born or late fetal stages seems unjustifiable. The intrinsic physiological properties, under normal experimental conditions, of young skeletal muscle—as in the 16-day rat embryo—therefore as yet are unknown.

Our experiments have produced evidence that potential neuromuscular conduction, at least on the efferent side, already is established in rat fetuses in the first half of the 16th day of gestation. Primitive nerve-terminations are present within the muscles of the forelimb, but it is extremely unlikely

* The possible effect of the surrounding fluid on the response likewise should be taken into account. It cannot be estimated, but apparently it exerts some buoyant effect that conceivably may modify the duration of a movement: for when the fetuses are removed from the bath they tend to flatten out, while the limbs so adhere to the trunk that visible somatic responses to stimulation cannot be elicited.

that any definitive nerve-endings have as yet been formed. At this stage, then, there exists the capacity for effective neuromuscular transmission in the absence of intimate connection between striated muscle and nerve. One therefore cannot ignore the possible rôle of nerves even in direct stimulation of the muscles in these young fetuses. It would seem desirable, moreover, to discard the term "myogenic" used by some authors to denote the earliest visible contractions that follow direct stimulation of fetal mammalian striated muscle (1, 2, 3, 30). This term is misleading, since no unequivocal proof of a purely "myogenic" stage of activity of striated muscle in mammals, as contrasted with "neurogenic," exists. Kuo (11) takes a similar stand. His conclusion (12), based on the effects of curare, that all somatic movements in young chick embryos are nervous in origin and that the skeletal muscles are incapable of activity without functional nerves, appears unconvincing, however; for he has assumed, without adequate evidence, that the reactions of embryonic and adult tissues to the drug are identical. Paton (19) observed somatic movements in embryos of the selachian *Pristiurus melanostomus* prior to innervation of the skeletal musculature as judged by the presence of neurofibrils following silver impregnation; but since he found "undifferentiated protoplasmic bridges" between spinal cord and myotome, Paton left the nature of the movements, whether myogenic or neurogenic, an open question. Possibly conditions differ among the various classes of vertebrates, but as yet there is no conclusive evidence that striated muscle ever includes an aneural active phase in its normal development.

It was noted that in some cases the forelimb muscles of 16-day-old rat fetuses appeared more readily excitable through their nerves than by direct stimulation. Our findings possibly imply a difference in chronaxies of muscle and nerve in young fetuses; or they merely mean that a direct stimulus sometimes may be too localized to produce more than a feeble, imperceptible contraction, whereas indirect stimulation, exciting a large number of nerve-fibers, provokes a more widespread, visible reaction.

A discussion of prenatal reflex activity lies outside the scope of this paper. But the possibility that some of the muscular responses in fetuses of this age are true reflexes, cannot be ignored. Since the dorsal spinal roots are well-developed, some of the nerve fibers within the muscles may well be of an afferent type. Windle and Baxter (29) found that morphologically complete reflex arcs already exist at this time. All of our results, however, appear capable of explanation with reference to efferent nerves alone, and we have observed nothing that can be termed reflex activity without question.

Summary

The earliest visible contractions of skeletal muscle in the living, intact rat fetus were produced by electrical stimulation during the 16th day of gestation. These involved a variety of forelimb movements.

The movements typically exhibited high threshold, relatively long duration (especially of the phase of relaxation), tendency toward rapid fatigue,

and long time factor (suggestive of both long latent period and long chronaxie of the muscles).

The limb at this stage is in a state of early differentiation, including not only muscle-fibers but also fascia, tendons and joints. This strongly suggests that extramuscular factors may be influencing the nature of the muscular response, whose visible properties thus may be more apparent than real. It is concluded, therefore, that the somatic movements cannot be unequivocally accepted as reflecting the physiological capacities of the muscles involved.

Evidence is presented indicating that potentially effective neuromuscular transmission, on the efferent side at least, exists in 16-day rat fetuses, although the nerve-endings themselves are primitive in form.

The theory of a "myogenic" developmental phase of muscular activity is discussed, and it is concluded that no valid evidence for such a phase exists.

This communication is based chiefly on work done at University College, London. We are greatly indebted to the late Professor H. H. Woollard, F. R. S., for the facilities of his laboratory and for his great interest in, and encouragement of, this work.

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